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EFFECTS OF HIGH-VOLTAGE CATHODE RAYS ON THE SKIN OF THE RAT*

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In December, 1926, W. D. Coolidge [1] of the General Electric Company described a new form of Lenard tube capable of producing a powerful beam of cathode rays or high velocity electrons in the air outside the tube.

In view of the extraordinary effects of the cathode rays on various inorganic and organic substances, it seemed of moment to study thoroughly the effects of the rays on living animal tissue. Coolidge and Moore [2] briefly described a few experiments to determine the gross effects of the cathode rays on the shaved ear of the rabbit and on bacteria. The reaction in the rabbit's ear varied from a slight tanning of the skin to complete destruction of the tissues throughout the entire thickness of the ear, depending on the time of exposure and the amount of current used. Quoting from the same article, the procedure was as follows:

Two circular areas one centimeter in diameter on the ear of a gray rabbit were exposed for one tenth of a second and one second respectively, at a

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* This is the first of a series of studies concerning the biologic effects of cathode rays which is in progress in this laboratory. The writers are under the greatest obligation to Dr. W. D. Coolidge, assistant-director of the research laboratory of the General Electric Company, Schenectady, N. Y., for placing the facilities of his laboratory at their disposal, and for his stimulating interest in all phases of the experimental work. The discussion of the physical aspects of the action of the cathode rays, which is somewhat interwoven into this report, is largely his own expression of that phase of the problem.

1. Coolidge, W. D.: The Production of High-Voltage Cathode Rays Outside of Generating Tube, J. Franklin Inst., December, 1926, p. 693.

2. Coolidge, W. D., and Moore, C. N.: Some Experiments with High-Voltage Cathode Rays Outside the Generating Tube, J. Franklin Inst., December, 1926, p. 721.

distance of two and one half centimeters from the window of a tube operating at one milliampere and 200,000 volts. The rabbit was confined in a wire netting cage metallically connected to the anode end of the tube, and the unexposed portion of the ear, as well as the remainder of the rabbit, was protected by a metal sheet with a circular hole in it. The rayed areas immediately became inflamed and within a day or so were covered with scabs formed from an exudate coming from the rayed tissues. When the scabs fell off a week or two later the hair came off with them, and for a while bare skin remained. The hair follicles had not been destroyed, however, for about three weeks later, hair grew again. But some change had taken place in the hair follicles, for on an area exposed for one second, the hair was now snow white and eventually grew to be about twice as long as the surrounding gray hair. . . . A third area, on the other ear of the same rabbit, was exposed for fifty seconds under similar conditions. In this case a scab formed on both surfaces of the ear and when the scabs eventually came off, a circular hole was left in the ear. White hair finally grew around the edge of the hole.

The foregoing experiments were made on the shaved ear. A ten seconds' exposure of the unshaved skin of the lateral abdominal wall of the rabbit gave the same effect as an exposure of one second on the shaved skin of the ear.

Plate cultures of *Staphylococcus aureus, B. coli, B. prodigiosus* and *B. subtilis* were killed by an exposure of 0.1 milliampere at 90,000 volts for one second, at a distance of 1 cm. from the window. The tube for these experiments was equipped with a 0.0127 mm. window of aluminum and was operated from high voltage direct current at constant potential.

The object in the first group of experiments was to study the effect of various doses of cathode rays on the skin. In order to facilitate the technical procedures the white rat was chosen as the experimental animal, a method for handling the rat in front of the tube having been developed by Prof. Arthur Knudson and Hubert Tanis, Jr., in connection with the former's investigation of the antirachitic value of the cathode rays. In each case, the entire rat was covered with copper foil, with the exception of an area 2.5 cm. in diameter on the anterior part of the abdomen, at which the rays were directed. In each instance the animal was held 2.5 cm. from the window of the tube.

In these experiments, the tube was operated from an induction coil, with a mercury turbine interrupter driven at such a speed as to give about 60 current impulses per second through the tube. Three voltages were used: 100,000, 200,000 and 350,000. These are maximum or peak values, and they were determined by sphere-gap measurements. The largest number of rats, twenty-four out of thirty-six, were exposed to 200,000 volts, six each to 100,000 and 350,000 volts. The length of exposure varied from one tenth of a second and six seconds repeated daily, to single rayings of six, eight, ten, thirty and sixty seconds. All of the animals here reported were killed by chloroform at different intervals, varying from three hours to fourteen days after the raying.

As will be seen from the effects subsequently shown, important observations are still lacking to make the series more nearly complete. For instance, there are no data concerning the chronic effects of the cathode rays, fourteen days being the longest interval before the tissues were examined. Another series of rats is being studied to show the later changes, which should be of great interest in view of the insidious development of the lesion of the skin caused by the roentgen ray. Observations of the effects of single exposures of short duration, from fractions of a second to five seconds, are also missing. The changes seen in the thirty-six rats in the present series, however, are of such nature that a fairly accurate picture can be given of the development of the cathode-ray skin "burn."

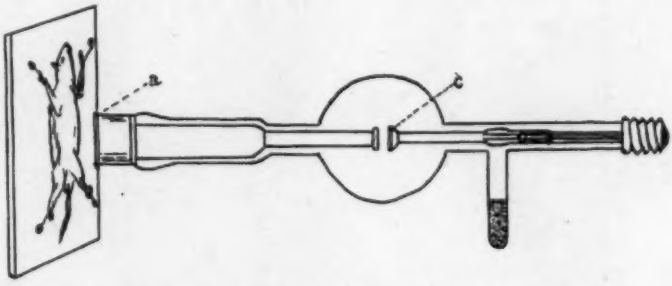

Fig. 1.—The Coolidge cathode ray tube, showing position of the rat with reference to the anodal window; *c* indicates the cathode, *a*, the anode, which is at the same time the window. The rat was 2.5 cm. from the window in each experiment, but was entirely shielded by copper foil except for an exposed area on the abdomen.

Data on Experiments on Thirty-Six Rats

Number of Rats	Date	Dose, Seconds	Frequency of Exposure	Killed
		100,000 Volts		
3	10/29	1	Daily 2 weeks	11/12
3	11/ 5	6	Daily 2 weeks	11/19
		200,000 Volts		
4	10/16	1/10	Daily 2 weeks	10/30
2	10/16	6	One	10/30
1	11/ 5	8	One	11/ 7
1	11/ 5	8	One	11/10
2	11/ 5	10	One	11/ 7
2	11/ 5	10	One	11/10
1	8/16	10	One	8/26
2	8/16	10	One	8/31
1	8/16	10	One	9/ 2
1	11/29	30	One	11/31
3	11/12	30	One	11/14
3	11/12	30	One	11/19
1	11/29	60	One	11/31
		350,000 Volts		
6	1/26	30	One	3 hours later

EXPERIMENTS

Six rats were given one exposure of thirty seconds with 350,000 volts, 1 milliampere, at 2.5 cm. distance from the window. The white hair over the exposed area on the anterior abdominal wall at once became yellow and the skin obviously tender. The animals were irritable after the raying, the hair of the entire body being fluffed up. During the raying there was a generalized muscular spasm which relaxed at once when the current was shut off. The immediate slight indisposition may have been due in part to the exhaustion produced by the muscle spasm. The results were the same in practically all the rats, the severity of the

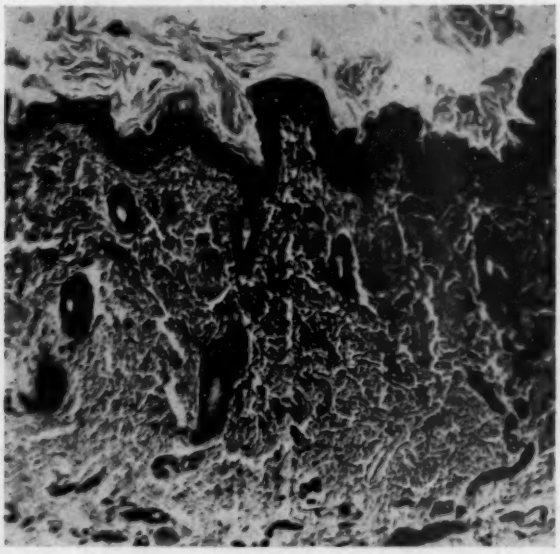

Fig. 2.—A section of the normal rat's skin on the anterior abdominal wall. This and all succeeding sections were photographed after having been stained with Mallory's phosphotungstic acid-hematoxylin; × 275.

reaction being roughly proportional to the length of exposure and the amount of current used.

The rats exposed to 350,000 volt rays were killed by chloroform three hours after raying. The hair, while changed in color, was still firmly attached to the skin. The epidermis was reddened and slightly dry. The entire abdominal wall in the area exposed and about 1 cm. beyond was removed and fixed in Zenker's fluid. Sections were stained with hematoxylin and eosin, methylene blue and eosin, Verhoeff's elastic tissue stain, Mallory's aniline blue-acid fuchsin and phosphotungstic acid-hematoxylin.

The histologic changes produced in the skin and subcutaneous tissues are shown in figures 3, 4 and 5. The epidermis in places had lost its

attachment to the corium except where it was anchored by hair follicles. In other areas the horny layer alone was stripped off, and there was a general excess of desquamation. The epidermal epithelial cells in all layers had lost their sharpness of cytoplasmic outline and the intercellular bridges had disappeared. The nuclei were a trifle shrunken and most of their chromatin was gone. The nucleolus in some cells could still be seen faintly.

The changes beneath the epidermis were largely confined to the corium, but they were also manifest in a slight degree in the connective

Fig. 3 (rat 7).—Appearance of the epidermis three hours after raying with 350,000 volts, during an exposure of thirty seconds. The epidermis has separated from the corium except where it is anchored by a hair follicle. The collagen of the corium is swollen, beginning to fuse, and streaks of basic staining fused collagen are visible; × 375.

tissue of the tela subcutanea. A remarkable effect was seen in the collagen fibers of the corium. They had become swollen and hyaline and later had fused; judging by their new staining properties, they had undergone a profound chemical change. Where they had fused, they stained an intense black with hematoxylin, blue with methylene blue-eosin and orange yellow with aniline blue-acid fuchsin. Between the altered collagen bundles, shadowy forms of fibroblasts and wandering cells were visible. The hair follicle epithelium showed degeneration, cytoplasmic shrinkage, pyknosis and karyorrhexis. The hair was somewhat

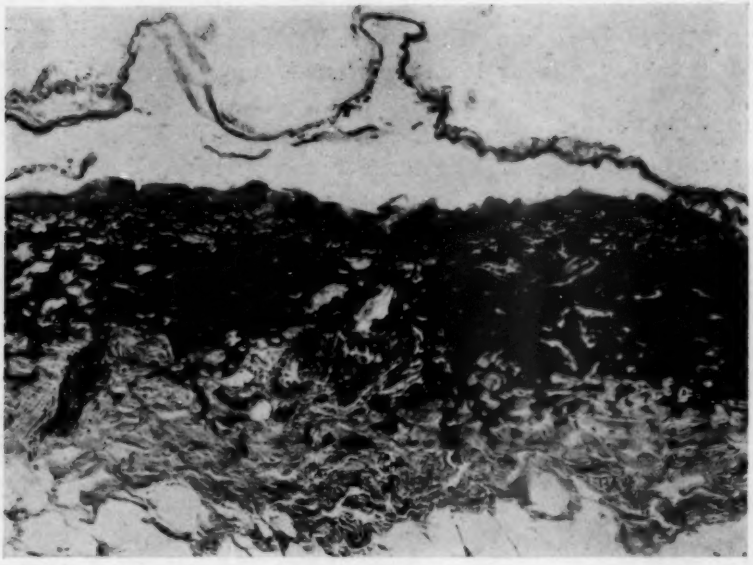

Fig. 4 (rat 9).—Appearance of the epidermis three hours after raying with 350,000 volts during an exposure of thirty seconds. The horny layer is being shed, but the remainder is still in contact with the corium. The zone of basophilic fused collagen measures in the picture 0.1 mm; × 325.

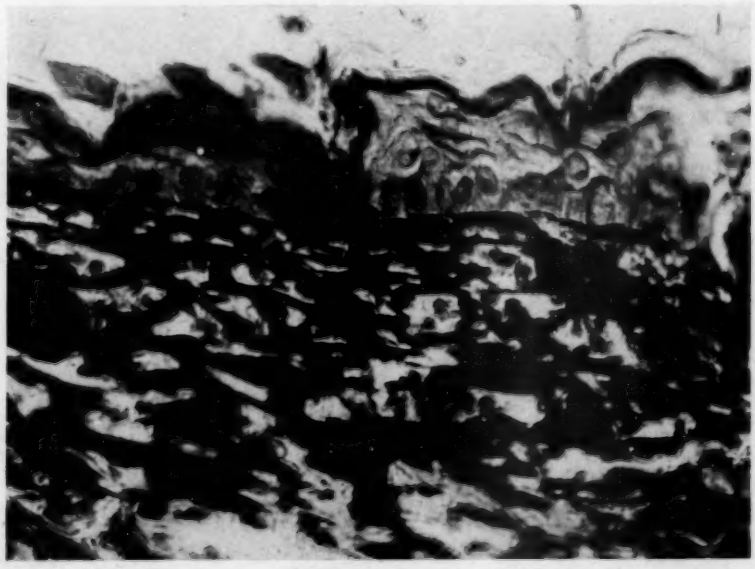

Fig. 5 (rat 9).—Cell outlines in the epidermis are indistinct. Shadows of nuclei are visible, but the chromatin has largely disappeared. Nuclei, probably fibroblast, are present in between the coarse masses of fused collagen: × 1400.

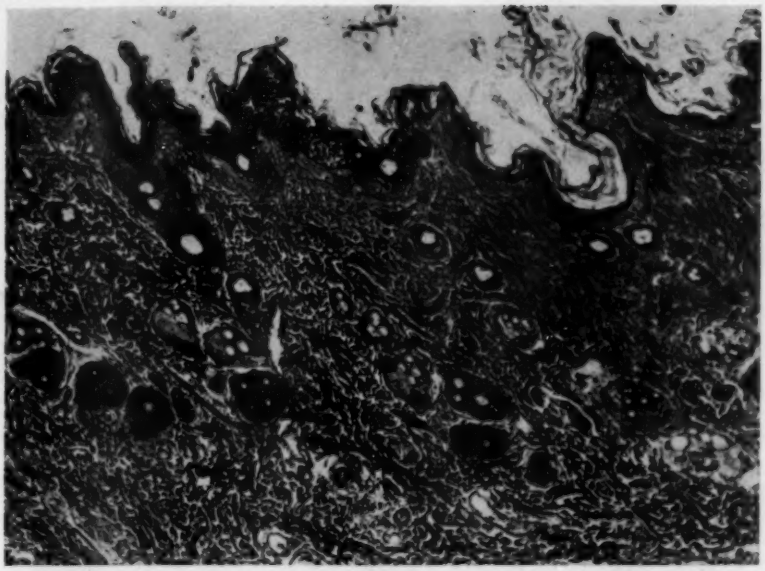

Fig. 6 (rat 701).—Appearance of the epidermis two days after raying with 200,000 volts during an exposure of ten seconds. The section is taken at the periphery of the burn. To the right the epidermis and hair follicles are shrunken and the connective tissue of the corium and deeper layers is beginning to swell and become more compact. To the left there is an intracutaneous collection of leukocytes, a not infrequent occurrence. Reduced from a magnification of × 375.

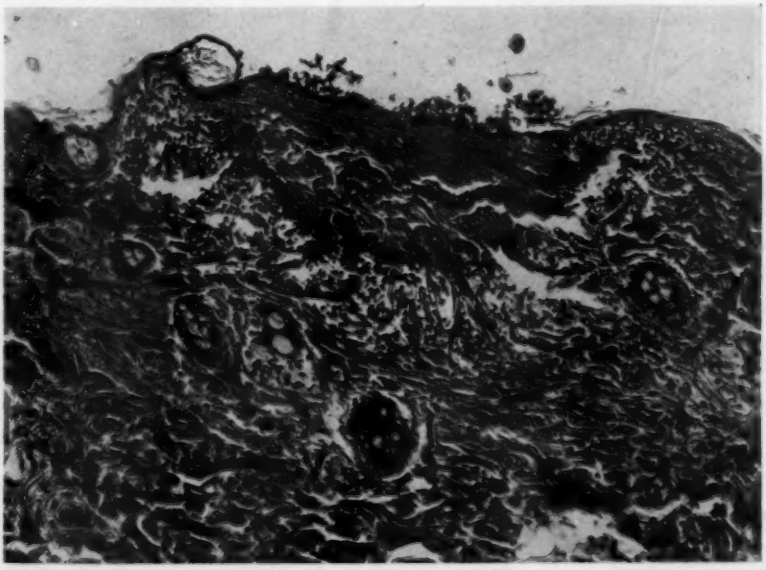

Fig. 7 (rat 699).—Appearance of the epidermis two days after raying with 200,000 volts, during an exposure of eight seconds. This shows the mode of separation of an area of necrotic collagen, leukocytes digesting the lower zone of dead tissue. Reduced from a magnification of × 375.

fragmented and pulled away from its sheath. The blood capillaries were contracted and recognized with difficulty in the corium, but the elastic fibers could not be identified.

The greatest alteration of the collagen lay in a zone about 0.1 mm. in thickness, but swelling and hyaline changes, "glassige verquellung," could be seen in the fibers in the upper portion of the tela subcutanea.

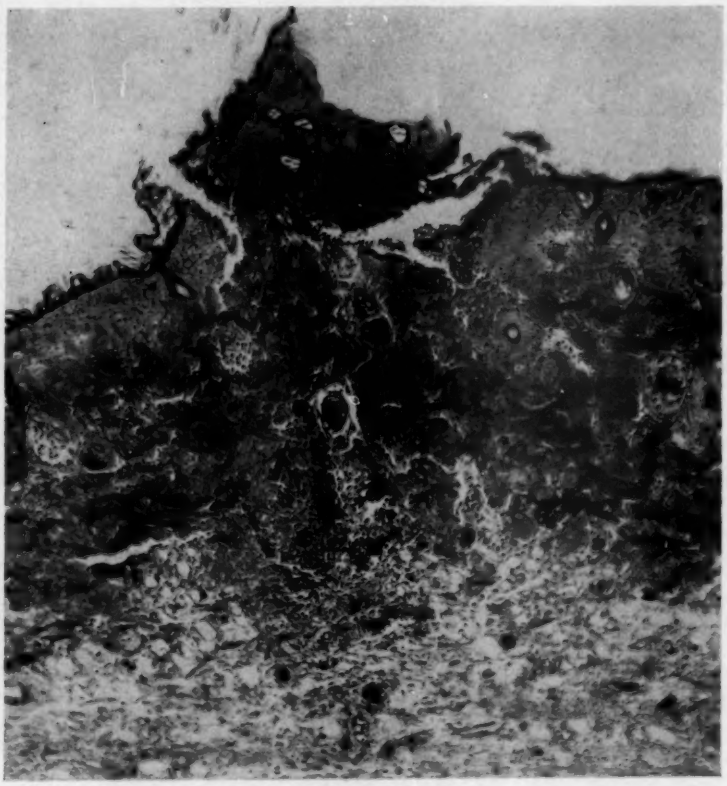

Fig. 8 (rat 716).—Appearance of the epidermis three days after raying with 200,000 volts, during an exposure of thirty seconds. A small connective tissue slough is nearly detached by leukocytic action. Swelling and coalescence of collagen bundles in the deeper tissues is evident, also degeneration of hair follicles. There is leukocytic invasion of subcutaneous fat; × 300.

The fat and abdominal muscle did not show any change. There was not any cellular infiltration about the injured tissue.

RAT 701.—One exposure of ten seconds to 200,000 volts was given. The rat was killed two days later. The epidermis showed much desquamation, but it was essentially intact although shrunken to about one sixth of its original thickness. The epithelium no longer stained distinctly and appeared as a line of fused cells which had lost their nuclei. The collagen of the corium was

swollen and beginning to fuse. All fibroblasts and other nucleated cells had disappeared. The elastic fibers had probably undergone changes similar to those in the collagen as they could not be recognized. The hair follicle epithelium was shrunken and colorless. The hairs also were shrunken. At the edge of the "burn" (fig. 6), a rather sharp line separated the rayed from the unrayed area, showing in this instance little evidence of spreading of the rays. In the cutaneous border, the superficial epithelial layer was necrotic and leukocytes had accumulated in foci somewhat resembling intracutaneous abscesses. The corium adjacent to the rayed field was being infiltrated with phagocytes. The blood vessel endothelium stained faintly, but there was no thrombosis. Slight interstitial edema was present.

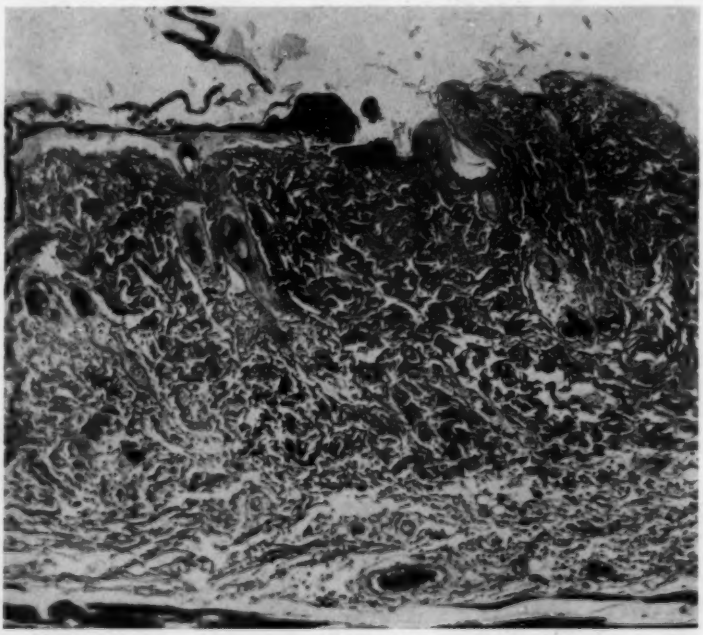

Fig. 9 (rat 700).—Appearance of the epidermis five days after raying with 200,000 volts, during an exposure of ten seconds. A thin layer of epidermal cells is still present, but held by hair follicles. The zone of altered collagen is plain although its lower limits are ill defined. The deeper blood vessels are dilated; × 250.

RAT 699.—One exposure of eight seconds to 200,000 volts was given. The rat was killed two days after raying. Changes similar to those in rat 701 were present; in addition, there were shown in small foci what happens to an area of degenerated collagen (fig. 7). Phagocytes had appeared in large numbers, digested the periphery of the collagenous mass and gradually isolated it from the underlying, more healthy tissue. Leukocytes had invaded many hair follicles, including some which were more deeply situated than the lowest border of the slough.

RAT 716.—One exposure of thirty seconds to 200,000 volts was given. The rat was killed after three days. The epidermis presented a loosening of the

upper layers and much desquamation of dead cells. In places, small portions of skin and corium were being sloughed off by the digesting action of phagocytes in a zone of degenerated collagen (fig. 8). There was marked glassy swelling of collagen with fusion of many bundles. Hair follicles undergoing shrinkage of the upper portions and hydropic swelling with nuclear pyknosis were seen in the lower levels. The hairs had fallen out at the level of the skin. Thrombosis of dilated capillaries occurred in the lower corium and the tela subcutanea. Edema and cellular infiltration had taken place in the subcutaneous fat and superficial muscle layers.

Fig. 10 (rat 714).—Appearance of the epidermis seven days after raying with 200,000 volts, during an exposure of thirty seconds. Much the same picture as is seen in figure 9, except that the layer of altered collagen is more sharply defined, is more deeply stained, and measures 0.22 mm. There is also slight shrinkage; × 250.

Rat 700.—One exposure of ten seconds to 200,000 volts was given. The rat was killed after five days. In the area directly exposed to the cathode rays, the epidermis had lost its horny layer and the malpighian layer was shrunken and devoid of nuclei, and the cell borders were indistinct. The collagen of the corium and upper tela was swollen and beginning to fuse. This layer of altered collagen was also beginning to take a deeper stain with hematoxylin (fig. 9). The hair follicles stained poorly, and the hairs were fragmented. Phagocytes were infiltrating the deeper corium from below. Blood

vessels were dilated, and there was moderate edema in the tela subcutanea. At the border of the exposed area, the epidermis was attached to the corium only by hair follicles, but some of the cells still stained fairly well. Masses of fibrin and necrotic epithelium projected over the rayed surface at its periphery.

RAT 714.—One exposure of thirty seconds to 200,000 volts was given. The rat was killed after seven days. A picture was seen much like that of rat 700, but the tissue was a little dryer and shrinkage increased (fig. 10). The altered collagen stained more deeply, and fusion of fibers was more pronounced. Fibroblastic activity did not occur. Phagocytes were entering the lower layers.

RAT 717.—One exposure of thirty seconds to 200,000 volts was given. The rat was killed two days later. The surface was dry, but some hairs were still present although many were falling off. There was a yellowish discoloration

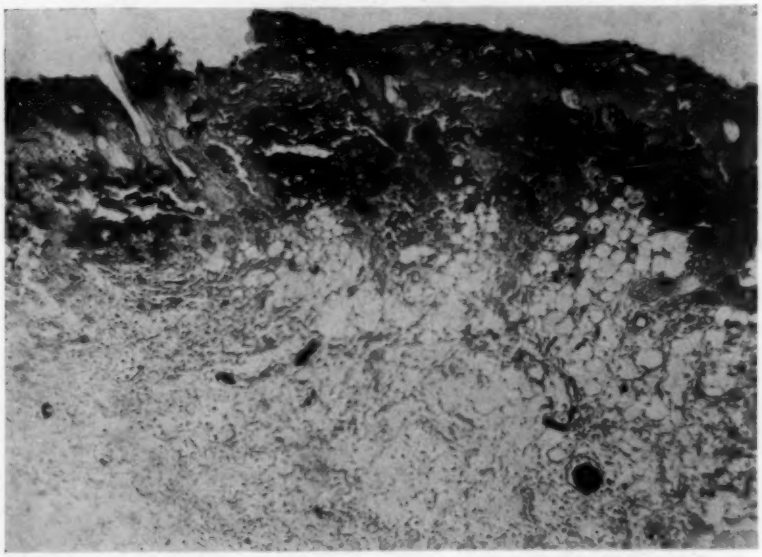

Fig. 11 (rat 717).—Appearance of the epidermis two days after raying with 200,000 volts, during an exposure of thirty seconds. The layer of necrotic skin and subcutaneous connective tissue extends to the fatty layer. Hair follicles and all other structures are involved in the burn. This layer is 0.14 mm. thick in the picture, but much shrinkage and drying have occurred. Edema and leukocytosis in the fat may be an indication that the rays have directly affected that tissue also. Reduced from a magnification of × 225.

of the hair. Histologically, the epidermis, corium and upper tela subcutanea had undergone acute necrosis, the upper and lowest layers staining black with hematoxylin. Hair follicle epithelium was destroyed, and hairs which were shrunken appeared to lie free in their sheaths. Blood vessels could not be recognized in this zone, as the tissue, except for the hair follicles, was fused into a mass of amorphous material. Beneath this layer marked edema and congestion were seen (fig. 11).

RAT 735.—One exposure of sixty seconds to 200,000 volts was given. The rat was killed two days later. The depth of necrosis was much like that of

rat 717; it was about 0.1 mm. in both animals. The necrotic tissue stained more uniformly an intense black with hematoxylin, however, and the hair follicles and other skin appendages were unrecognizable. There were marked edema and congestion with precipitation of fibrin in the tela subcutanea, abdominal muscle and underlying fascia. Beginning fragmentation of superficial muscle fibers was seen (fig. 12).

RAT 703.—One exposure of ten seconds to 200,000 volts was given. The rat was killed after two days. The epidermis was necrotic and shrunken, but only the superficial horny layer had desquamated. Hairs were still present

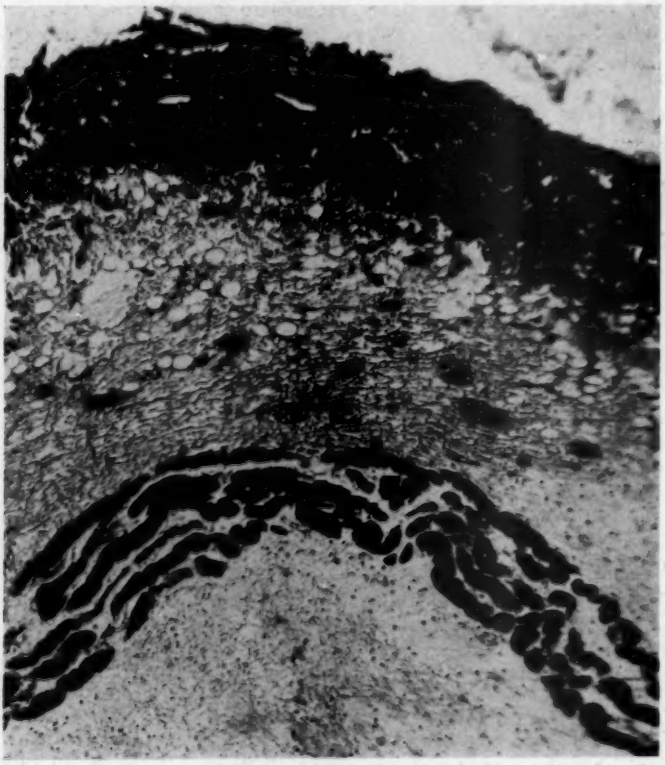

Fig. 12 (rat 735).—Appearance of the epidermis two days after raying with 200,000 volts, during an exposure of sixty seconds. The section is much like that in figure 11, although the longer exposure here has converted the upper layers (0.13 mm. in the picture) into a mass of basophilic amorphous material. The upper layer of fat cells has also undergone necrosis and there is marked edema of the rest of the abdominal wall. Reduced from a magnification of × 205.

in follicles, although the follicular epithelium in the upper third was fused into a blackish staining mass. The corium showed swelling and fusion of collagen fibers, but the limits of this change were ill defined. Capillary dilatation, swelling of the endothelium and some thrombosis were present. Muscle bundles and fascia were infiltrated with various types of phagocytic cells (fig. 13).

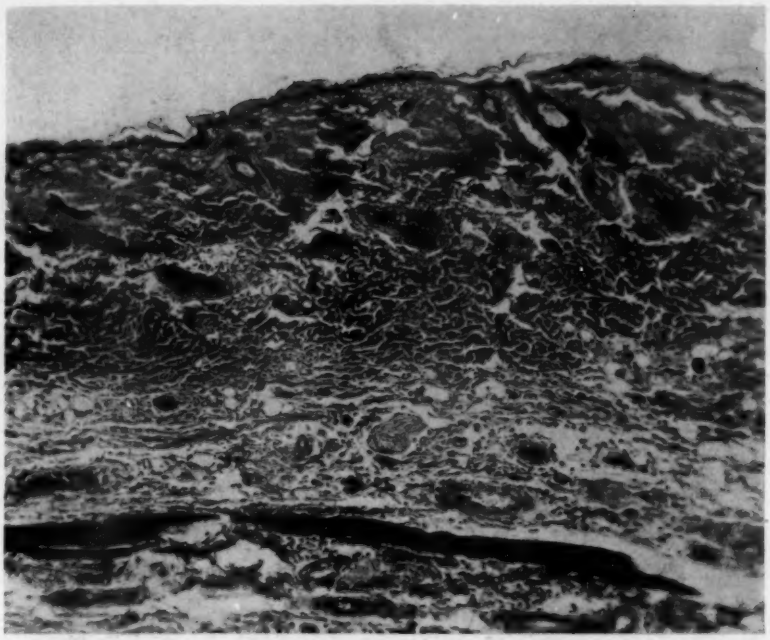

Fig. 13 (rat 703).—Appearance of the epidermis two days after raying with 200,000 volts during an exposure of ten seconds. The epidermis is necrotic and shrunken. The collagen of the corium is swollen; the fibers are apparently fusing. There is dilatation of blood vessels and some thrombosis and leukocytic infiltration in the deeper layers; × 245.

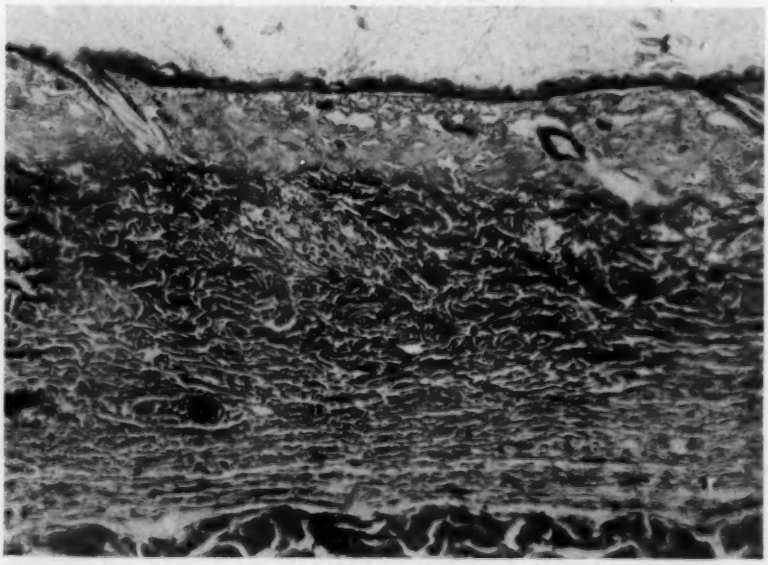

Fig. 14 (rat 702).—Appearance of the epidermis five days after raying with 200,000 volts, during an exposure of ten seconds. The epidermis is shrunken and necrotic. A layer of collagen about 0.1 mm. thick is almost entirely fused, but at this stage is more acidophilic than basophilic. Reduced from a magnification of × 270.

RAT 702.—One exposure of ten seconds to 200,000 volts was given. The rat was killed after five days. The epidermis was desquamating, and the malpighian layer was beginning to separate from the corium in many places. The epithelium of hair follicles had undergone degeneration. The zone of swollen and fused collagen in the corium was well defined, in contrast to the picture in rat 703. There was practically no fibroblastic activity. Leukocytes were present in moderate numbers in the tela subcutanea. The capillaries were dilated. The muscle was normal (fig. 14).

RAT 662.—The rat was exposed six seconds daily for fourteen days to 200,000 volts, and then killed. A narrow zone of degenerated collagen was still visible, and the epidermis had been sloughed off (fig. 15). At the border of the rayed area, the epidermis was split into several layers; the lowest, where

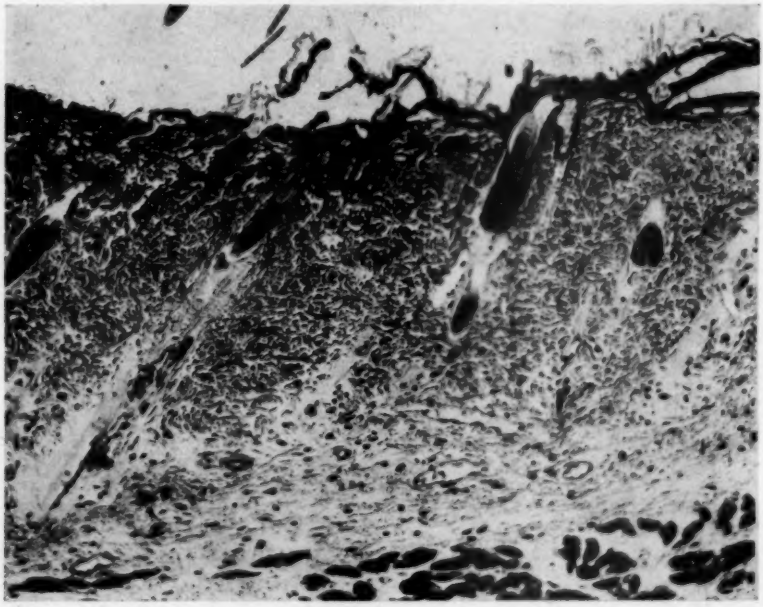

Fig. 15 (rat 662).—Appearance of the epidermis of a rat exposed to 200,000 volts for six seconds daily for fourteen days, then killed. A narrow zone of necrotic collagen is seen at the left, which is devoid of epidermis. There is separation in the layers of adjacent epidermis; the fibroblasts are active in the deeper layers; the blood vessels show little change; × 275.

it still was in contact with the corium, contained viable cells. The deeper layers of the corium showed slight swelling of the collagen, and hair follicles had undergone degeneration, but there were less marked changes as a whole than in the upper levels. Marked edema with fibrin precipitate was present in the tela subcutanea and muscle wall. The leukocytes were moderately numerous, and there was definite, although slight, fibroplasia. The blood vessels showed insignificant changes.

RAT 4.—One exposure of ten seconds to 200,000 volts was given. The rat was killed fifteen days later. A large slough had formed which extended down

to the muscle bundles. Many muscle fibers had become necrotic and disappeared; others showed little more than their sarcolemma sheaths. There was some regeneration of hair follicle epithelium, but little evidence of epithelial repair at the periphery of the "burn." The capillaries were dilated; many were thrombosed, although the endothelium presented little change. There was moderate leukocytic infiltration (fig. 16).

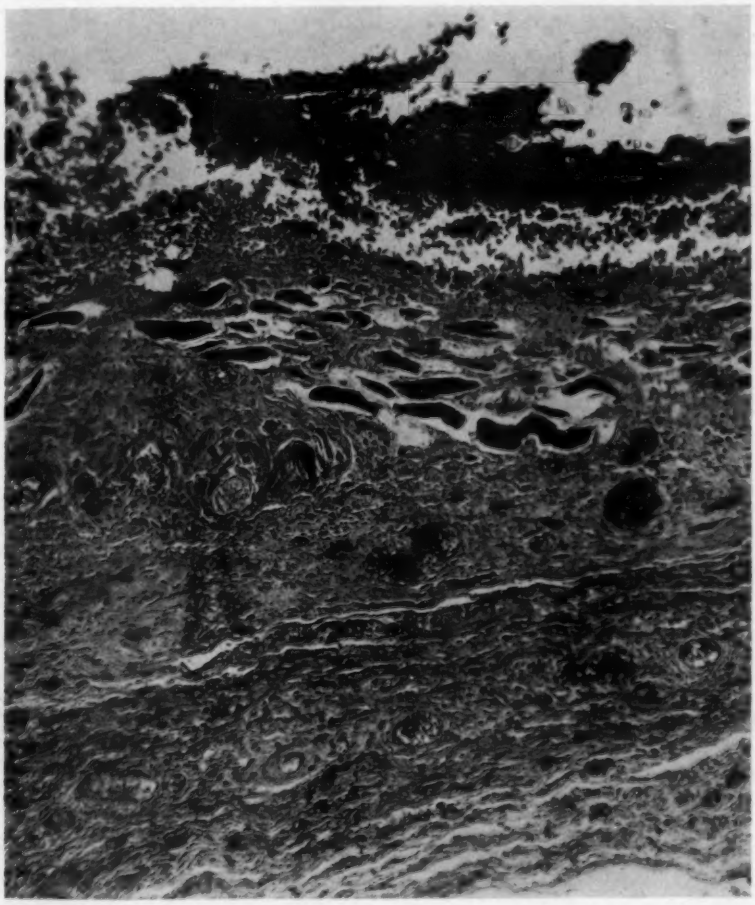

Fig. 16 (rat IV).—Appearance of the epidermis fifteen days after raying with 200,000 volts, during an exposure of ten seconds. A large slough extends down to the muscle which shows degenerative changes. The hair follicle epithelium shows evidence of repair but none over the wound. There is interstitial fibrosis in the muscle bundles; thrombosis of blood vessels; × 300.

Rat 665.—The animal was exposed for one tenth of a second daily for fourteen days to 200,000 volts and was killed on the fourteenth day. A large ulcerated surface of skin was seen with a dry scab on the exposed area. The floor of the ulcer consisted of dense, swollen collagen fibers which approached normal in staining properties. Dry fibrin and amorphous material overlay

the exposed corium. There was considerable shrinkage of the connective tissue down to the muscle wall, so that many blood vessels were compressed nearly to invisibility. Other vessels did not show any endothelial proliferation nor hyaline changes. Fibroblasts were moderately active, but chiefly in the deeper layers. Mononuclear phagocytes appeared in moderate number in the tela subcutanea. At the edges of the ulcer, the epithelium was thickened, and there was a beginning downgrowth from the basal layer. Mitotic figures were increased in number. The epithelium, while active at the edges, had not made any headway in covering the ulcerated surface (fig. 17).

Rat 660.—The rat was exposed one tenth of a second daily for fourteen days to 200,000 volts. It was killed on the fourteenth day. There was an ulcerated, slightly moist surface, with dried secretion in places. The epidermis had

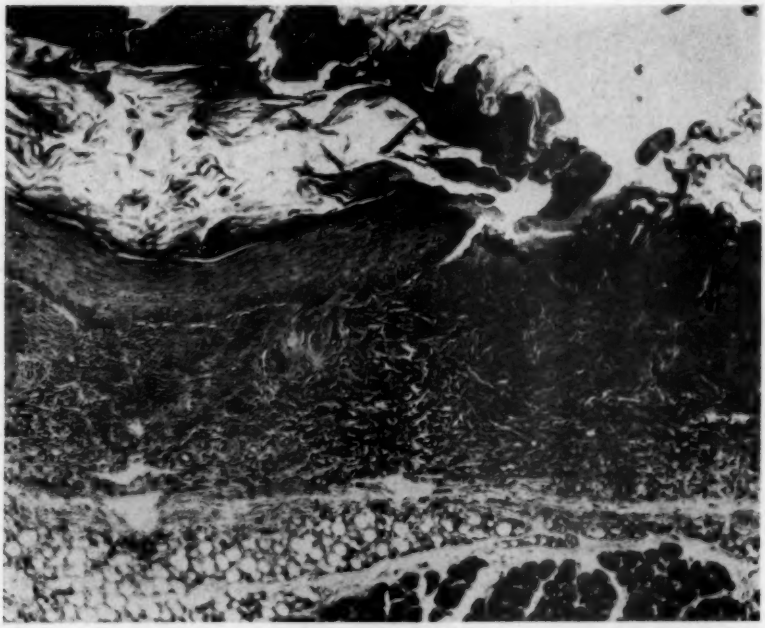

Fig. 17 (rat 665).—Appearance of the epidermis of the rat exposed to 200,000 volts, for one tenth of a second daily for fourteen days and then killed. The section is taken at the border of the ulcer. A thickened epithelial stub is proceeding with difficulty over the ulcer, the floor of which is of dense swollen collagen poor in cells. Reduced from a magnification of × 275.

disappeared and fully half the corium had sloughed off, exposing many hair follicles. The corium showed marked fibroblastic proliferation, but the blood vessels were practically normal. The hair follicle epithelium was destroyed, although portions of many hairs still were present in the degenerated sheaths. Foreign body giant cells were present in the bases of hair follicles, often clustered about fragments of hairs. There were small abscesses in some of the follicles. Marked invasion of the fat of the tela subcutanea by fibroblasts had occurred. Some new formation of capillaries was found in this layer. Edema was pronounced above the muscle layer. There was no evidence of epithelial repair at the edges (fig. 18).

RAT 666.—An exposure of one tenth of a second to 200,000 volts was given daily for fourteen days. The rat was killed on the fourteenth day. A few hairs were still attached to the skin, the surface of which was dry and covered in places by a crust. Microscopically, the epidermis could still be identified in many places, although in the center it had been destroyed and covered by a thick layer of amorphous necrotic material. Much scaling was taking place along the periphery. The most conspicuous lesion was a zone of necrosis in the lower corium, which had proceeded through the lower third of the hair follicles, thus separating a thick upper layer from the deeper corium. The actual separation had been accomplished by autolytic enzymes and in small part by leukocytic digestion. While the injury to the connective tissue was sharply outlined, the lower ends of the hair follicles showed epithelial necrosis

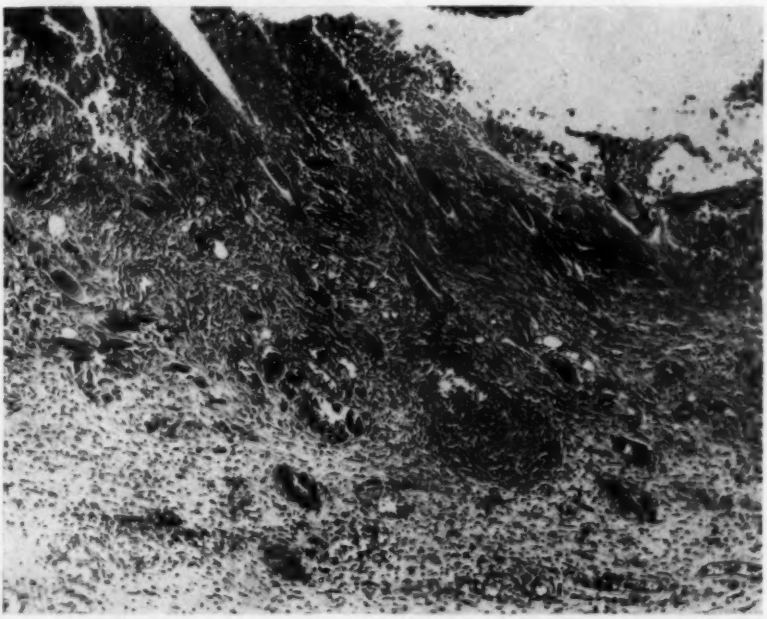

Fig. 18 (rat 660).—Appearance of epidermis of a rat exposed to 200,000 volts for one tenth of a second daily for fourteen days and then killed. The section shows an ulcer with its floor in the deeper corium, coated with exudate due to secondary infection. Many hair follicles are destroyed, foreign body giant cells attacking the follicles. Minute subcutaneous abscess and much leukocytic reaction and fibroplasia are present. Reduced from a magnification of × 275.

below the level of the slough (fig. 19). In this zone, the collagen was denser than normal and the fibers were swollen. The tela subcutanea was edematous and much fibrin was in evidence. Phagocytic cells were present in moderate numbers in this layer. The blood vessels were rather constricted, but did not show any endothelial proliferation or thrombosis. A moderate degree of fibroplasia was evident in the lower layers. The muscle was normal, except for slight edema. Near the periphery of the exposed surface in some areas, small connective tissue sloughs had occurred and a new growth of epithelium

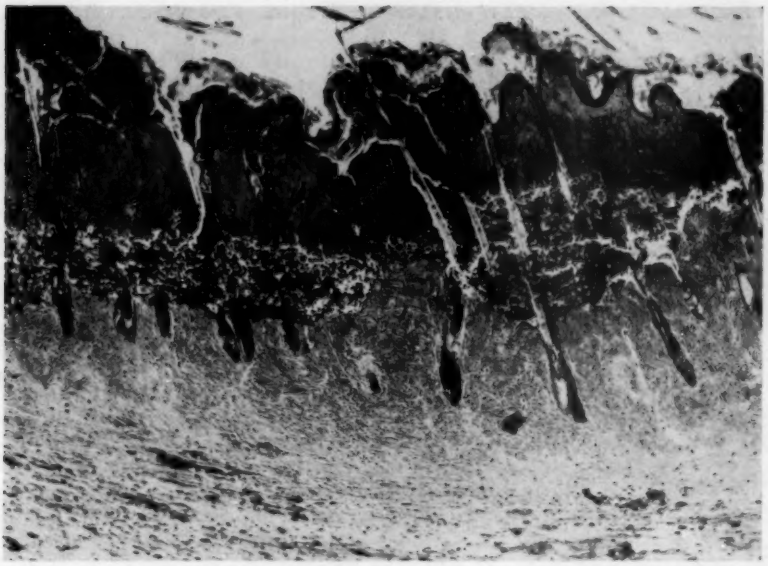

Fig. 19 (rat 666).—Appearance of the epidermis of a rat exposed to 200,000 volts for one tenth of a second daily for fourteen days and then killed. A deep corium slough is shown extending to about the level of the lower third of the hair follicles, the shafts and a narrow piece of collagenous tissue still holding the slough. Edema and fibrin precipitate are seen in the deeper tissues. Reduced from a magnification of × 275.

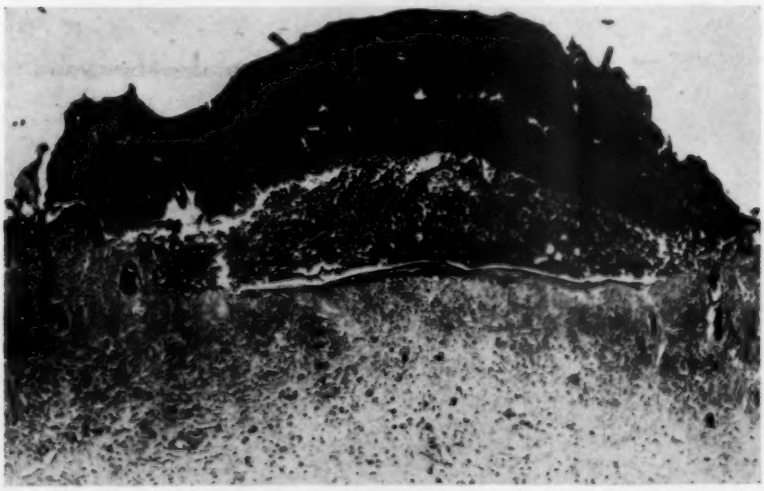

Fig. 20 (rat 666).—Another portion of the skin showing regeneration of epithelium beneath a small slough which is nearly separated from the skin. This was the most advanced healing of epithelium seen in this series of rats. Reduced from a magnification of × 225.

was taking place before the crust had actually become detached. This was the only rat in this series which showed this epithelial repair (fig. 20).

RAT 683.—The rat was exposed six seconds daily to 200,000 volts for fourteen days and was killed on the fourteenth day. The surface of the rayed area was dry and hairless. Microscopically, it was devoid of epidermis, although along the edges a dry epithelial crust could be recognized. The corium was exposed, and the hair follicles had disappeared in their entire length. The collagen bundles were large and coarse. In between them were small nuclei probably belonging to resting fibroblasts. There was slight mononuclear cell infiltration in the deeper layers and about the upper muscle bundles. The blood vessels were dilated although apparently decreased in number (fig. 21).

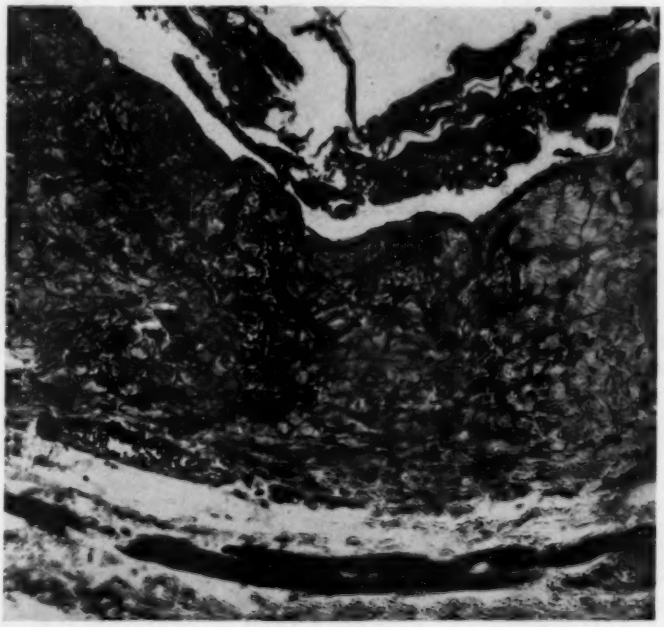

Fig. 21 (rat 683).—Appearance of the epidermis of a rat exposed to 200,000 volts, six seconds daily for fourteen days and then killed. The floor of the ulcer of dense collagen with many fibroblast nuclei is seen. The old epidermis is being desquamated, but there is no epithelial repair over the exposed corium. This might be considered a burn which is healed except for lack of a new epidermis; × 375.

COMMENTS ON EXPERIMENTS

As stated previously, this series of experiments with cathode rays is incomplete in several respects, particularly in the immediate and the more chronic changes in the cutaneous tissues. But even so far as we have gone, there is manifest difficulty in fully understanding the pathologic lesions, since we have few phenomena with which the tissue changes can be compared. Such high voltages as were used have not been

employed before in biologic work with cathode rays. Pauli and his co-workers may have reached 50,000 volts with their modified Lenard tube, and, interestingly enough, they have described tissue effects of the cathode rays which we are able to confirm in many details, and also to intensify to a degree not heretofore possible.

On the physical side, these experiments with the cathode ray are complicated. As the tube has been operated from a source of widely fluctuating potential, the electrons inside the tube, as they impinge on the window, will have a wide range of velocities. After passing through the window and the layer of air intervening between the window and the rat, their average velocity will have been somewhat reduced. The surface of the rat's skin will be subjected to bombardment by electrons ranging in velocity from zero all the way up to that corresponding to the maximum or peak value of the voltage applied to the tube. As the rays penetrate into the tissues, their average velocity decreases.

The rat is exposed not only to the primary cathode rays, but also to the roentgen rays produced by the impact of the cathode rays on the window, the window support, and the air between the rat and the window. The animal is also exposed to the roentgen rays produced within its own tissues by the impact of the cathode rays on the matter composing the tissues. It is also exposed to secondary cathode rays produced within its tissues by the roentgen rays.

The primary cathode rays have a limited range in the rat's tissue, amounting to only a few tenths of a millimeter and determined by the voltage applied to the tube. Their direct action will then be confined to a superficial layer. On the other hand with the voltages employed, the roentgen rays are penetrating, and the secondary cathode rays liberated by them will be produced throughout the entire thickness of the rat's body.

It is now generally assumed that the biologic effect of the roentgen rays is entirely due to the secondary cathode rays which they produce. If this is true, the lesions obtained in our experiments are due to primary cathode rays, confined in their range of operation to a superficial layer only a few tenths of a millimeter thick and to secondary cathode rays liberated throughout the entire thickenss of the exposed portion of the animal.

The direct effect of the primary cathode rays should be superficial, while that of the secondary cathode rays, originating as they do within the tissues, should decrease only slightly with the depth.

The range of the primary cathode rays in the tissues of the rat is of interest. Direct measurements have not been made, but the following consideration should give results of the right order of magnitude. At 200,000 volts and with a nickel window like that used in our experiments, the range of the cathode rays in air, as measured by the fluorescence of

lime, was found by Coolidge [1] to be 40 cm. At a distance of 2.5 cm. in front of the window (the distance at which the rat was placed in all of our experiments), the remaining range in air was $40 - 2.5 = 37.5$ cm.

Assuming that the superficial tissues of the rat have the same density as water and that the penetration of the cathode rays in various substances is inversely proportional to their density, the range of the 200,000 volt cathode rays in the tissues of the rat would be

$$\frac{37.5 \times 0.0012}{1.0} = 0.045 \text{ cm.}$$

By a similar calculation from data not yet published by Dr. Coolidge on the range in air at other voltages, the range of the 100,000 and 350,000 volt cathode rays in the tissues of the rat, placed 2.5 cm. in front of the window, would be 0.14 and 0.91 mm., respectively.

A study of the photomicrographs shows that the visible effect is limited to a depth considerably less than the calculated range. At 200,000 volts, for example, the visible effect is limited to a depth of perhaps 0.25 mm., while the calculated range is 0.45 mm. One would expect the depth of the direct effect of the primary cathode rays in general to be less than their range as measured by a sensitive indicator, such as lime, for the value assigned to the range will be greater, the greater the sensitiveness of the indicator.

The fact that the observed effect is so superficial indicates that it is due to the primary cathode rays and not to the secondary cathode rays resulting from the penetrating roentgen rays. This was to be expected from the energy relations; for the efficiency of roentgen-ray production is low, so low that probably less than 0.1 per cent of the energy involved is at any time in the form of roentgen rays.

The depth of penetration of the rays as measured by the photographs is far from accurate as the shrinkage of the tissue following raying and further shrinkage in the preserving fluids after death have not been computed. There was a closer approach to the theoretical limit than the figures indicate.

With the heavy doses employed in our experiments and in view of the profound chemical changes produced by cathode rays in many organic materials, we might expect to find evidence of chemical alterations in the tissues. Possibly new organic combinations could be detected by appropriate methods.

In the skin of rats 5 to 10 inclusive, which were killed three hours after exposure to 350,000 volt cathode rays for thirty seconds, a peculiar degeneration of the connective tissues of the corium is sharply outlined to a depth of about 0.1 mm. Rats exposed to other voltages and for shorter times showed a definite change in the collagen to about the same depth.

Hence it would seem permissible to believe that this acute effect in the upper 0.1 mm. of skin is due to primary cathode rays.

The epithelium of the shaved skin is probably killed at once by ten seconds exposure to 100,000 volt rays. An exposure of one second to 200,000 volts and upward will result in death of the cells of the epidermis, but several hours will probably be required before there is morphologic evidence of death. These statements are based chiefly on a study of rats 5 to 10, which were killed three hours after raying with 350,000 volts for thirty seconds. The epithelial cells of the stratum corneum and rete mucosum still retain their general shapes, and although the chromatin of the nuclei has largely been destroyed the nuclear membrane is apparently intact. The nucleolus can still be seen in some cells. The cytoplasmic cuticular border is less distinct and the intercellular "bridges" are no longer present. The cytoplasm is slightly opaque, and mitochondria cannot be stained. The eleidin granules are no longer visible. In the basal layers, there is possibly some diffuse hydrops of the cytoplasm.

Degeneration of the chromatin is likewise a prominent feature. It is a well known fact that the chromatin is greatly affected in roentgen-ray injury. Many agents, however, affect the chromatin, hence it cannot be said that these changes in the epithelium are not true effects of the cathode ray. Desquamation of epidermal cells increases rapidly in amount, but the lower degenerating or actually dead layers may remain in contact with the corium until the connective tissue slough is about ready to fall off. The degenerative changes in the connective tissues together with secondary vascular changes undoubtedly would lead to epidermal necrosis; but since the epidermis is the layer nearest the source of the rays, and since the acute degenerations appear so promptly and before any vascular injury can be seen, the epidermal lesions must be due to the direct action of the cathode rays and not to vascular-nutritional factors.

Small doses of cathode rays, such as 0.1 second daily for fourteen days, result in degenerative changes in the epidermis, the most conspicuous of which is a gradual shrinking of the cells of this layer until they almost lose their identity and are thrown off in sheets, leaving a denuded corium. Marked changes occur in the corium, but the blood vessels are not affected sufficiently to account for the necrosis, hence the lesions which develop during a fourteen day interval are also, without much doubt, actual radiation effects.

The fact that the hair follicles suffer more than the connective tissue at the same level, shows that epithelium is more susceptible to injury by the rays than is connective tissue. In some animals, before the connective tissue had shown any appreciable change the hair follicles were destroyed and the hairs fragmented, much in the manner of lightning following down the trunk of a tree.

In from two to fourteen days, phagocytes and foreign body giant cells had appeared around the necrotic cells, the cellular infiltration being most marked in those rats which had received multiple small doses rather than one long exposure.

In this series of animals, regeneration of epithelium at the edge of the wound was seen in only two instances, and then only after fourteen days. In one rat it was evidenced by a thickening of the epithelial border without any spreading out over the exposed corium. In the other, a few microscopic areas of regeneration in a thin sheet were present beneath the connective tissue slough. This almost complete lack of regeneratory response on the part of the epidermis would seem to indicate that the cells at the border, while not killed by the cathode rays, were much depressed from the standpoint of proliferation, or that toxic substances were present in the denuded corium of the rayed area where so much destruction had taken place. Possibly the p_H of the tissue or the formation of other inhibitory chemical substances was responsible for this failure of epitherial repair. It is a well known fact that burns due to roentgen rays and lightning also heal sluggishly; hence there may be an explanation for this cell depression common to these three types of injury due to radiation.

It would be well at this point to summarize the histologic changes produced experimentally in animals by roentgen rays. Wolbach [3] has studied the reactions in the skin of the rat and the guinea-pig. In his article, the dosage is not stated; he says only that it was sufficient to produce relatively acute changes in the skin and subcutaneous tissues. The earliest histologic lesion, he states, is a swelling of the collagen of the corium and subcutaneum, the fibrils coalescing to produce a compact refractive thickened corium. In guinea-pigs, this change is visible in from forty-eight to seventy-two hours after a single exposure, reaching a maximum in from six to eight days, with shrinkage of the skin.

The collagen effect is regarded as more or less specific and is seen also in the walls of the large blood vessels and in the stroma of the skin appendages. The swelling is thought to be due to difference in osmotic tension because of the presence of products of decomposition. A latent period intervenes and is the time during which the altered collagen and tissue liquids reach equilibrium. The epidermis does not show any change until after the swelling of the collagen, and is considered secondary to obliteration of lymph and blood capillaries. The altered collagen does not regenerate, but the surviving fibroblasts produce new collagen, which is laid down between the old fibers and causes much thickening of the corium. The epidermal changes are visible on the

3. Wolbach, S. B.: A Summary of the Effects of Repeated Roentgen-Ray Exposures Upon the Human Skin, Antecedent to the Formation of Carcinoma, Am. J. Roentgenol. **13**:139, 1925.

fourth day and consist of swelling and mitosis of the cells. The maximum effect is in the superficial corium, and only in this layer is there actual necrosis with polymorphonuclear cell reaction.

One is struck by the many qualitative resemblances between the effects of the cathode ray and those Wolbach found with roentgen rays. It is of especial interest to note what he calls the specific effect of roentgen rays—the swelling and coalescence of collagen in the corium. If we should attempt to name a specific, constant lesion in the rats exposed to cathode rays, it would also be a swelling and fusing of the collagen of the corium. At higher voltages, i.e., 350,000, other changes also occur with liberation of products of an acid nature.

At a depth of about 0.1 mm., apparently, fibroblasts do not survive; in fourteen days repair by fibroblasts occurred slowly and from below, so that thickening of the corium was not observed. The swelling of the collagen in our animals could be interpreted also on the basis of establishing osmotic equality in the presence of crystalloidal products of decomposition.

It is difficult to explain the epidermal changes caused by cathode rays as being secondary to obliteration of blood vessels, as Wolbach postulated for his roentgen-ray effects. The cathode particles actually strike this layer and kill the cells quickly. The application of 350,000 volt rays for thirty seconds in three hours caused the epithelium of the epidermis and its appendages to lose their sharp cell outlines, to become swollen, and the nuclei to lose most of their chromatin. After from twenty-four to forty-eight hours, this layer had become shrunken and separated at many points from the corium. At the same time, the collagen of the corium showed its peculiar swelling and coalescence of fibers. The blood vessels in the corium were contracted or entirely lost in the layer of altered collagen. The epidermal change in our animals is probably a direct effect of the impact of electrons. In both roentgen-ray and cathode-ray burns the necrotic collagen is in time invaded by leukocytes, and in the cathode-ray burns large corium sloughs are thrown off.

Pauli and his co-workers, in several articles which have appeared in German periodicals since 1919, have made a careful study of the effects of cathode ray on living tissue, but they have been restricted by experimental difficulties to relatively low voltage. Their observations will be reviewed in some detail. They used a modified Lenard tube with an aluminum window which is more transparent for a given voltage than the nickel window we used.

Von Angerer, Pauli and von Redwitz [4] studied the action of cathode rays on plant cells, bacteria in vitro and in fresh wounds, and reached the following conclusions: Temperature changes induced by the cathode

4. Von Angerer, C.; Pauli, W. E., and Von Redwitz, E.: Ueber die Einwirkung der Kathodenstrahlen auf Bakterien in vitro und in frischen Wunden, Deutsche Ztschr. f. Chir. **193**:333, 1925.

rays are not responsible for the tissue changes. Plant cells die or degenerate because of changes in the cytoplasm, not in the cell wall. Muscle and connective tissue show great resistance, but epithelial cells undergo marked degeneration and necrosis. Rats' eyes with ulcus serpens were successfully treated; one second of raying stopped the progress of the ulcer, which healed uninterruptedly without injurious side action.

In a depth of 0.1 mm., bacteria in a drop of pus were killed. Staphylococci were more resistant than *B. coli* in mixed cultures. Pauli and Hartmann [5] rayed pure cultures of *B. coli* and *B. proteus* in agar and bouillon. A trace of culture in a small drop of sterile medium was placed on a sterile slide and exposed to a variable number of discharges from the tube. Both bacteria were killed after from fifty to sixty discharges. A smaller number of discharges permitted growth in twenty-four hours. The bactericidal action was attributed to the cathode rays themselves. Heat action was excluded, and drying did not prevent growth in unrayed specimens.

Raying of algae caused a clumping of the chlorophyl granules, but Pauli and Hartmann called attention to drying, which was a source of error in their earlier experiments. They overcame this by coating the edges of the coverslip with paraffin. The chlorophyl granules disintegrated promptly. An overlying film of water protected the plant cells. The rayed cells were more influenced by temperature changes than were the unrayed cells.

The same workers exposed to the cathode rays the skin and muscle of the narcotized toad, *Bufo vulgaris* and *Bufo viridis*. After from one to two hours the muscle had lost its red color and took on a cloudy whitish appearance. Microscopically, there was only swelling of the muscle fibers. Significant changes were not seen in the connective tissue. When the skin of the back was rayed, a slight browning of the greenish skin occurred, and the green spots lost their sharp outlines. The skin became smooth, slightly dry and desquamated. Microscopically, the superficial portion of the horny layer of epithelium was raised with the formation in the middle layer of fluid filled spaces. Degenerations occurred in the basal layer also. These changes were noticeable three fourths of an hour after raying. If the raying was more intense, the entire epithelium was torn away, the subcutaneous connective tissue being exposed. The cells stained with difficulty; they became swollen and their nuclei pyknotic. Large spaces often formed in the epidermis which were filled with phagocytic cells. The connective tissue remained unaltered, although some infiltration with wandering cells took place. The cellular infiltration ran parallel with the intensity of raying and appeared after several hours. An increase in leukocytes was present in the vessels

5. Pauli, W. E., and Hartmann, A.: Ueber die Wirkung von Kathodenstrahlen auf lebendes Gewebe, Arch. f. mikr. Anat. **103**:95, 1924.

of the rayed area. The doses used did not prevent epithelial regeneration in from four to five days. The pigmented spots of the skin became pale, owing to the migration of chromatophores from their normal position. The glands of the skin at first secreted excessively, but later collapsed and disappeared.

They also found that in the amputation stump of the tail of *Triton taeniatus* epithelial regeneration began in six hours and was complete in twenty-four hours in the unrayed animal, but that raying of the stump produced epithelial degeneration without evidence of repair in twenty-four hours. Their experiments with the white mouse, however, probably furnish the best comparison with our work on the white rat. A stronger dose of rays was necessary to produce changes in the skin when the hair was present than when the hair had been previously removed. Macroscopically, the hair immediately became brown, the skin later became rough and scaly, and in twelve days smooth and shiny. Ulceration was never seen. The hair grew again only in a few animals. Microscopically, the injury was mainly epithelial, with small damage to the dermis. There was some infiltration with leukocytes. In a few cases, the compact connective tissue was thickened.

The surface epithelium became broken up into layers with leukocytic foci in the epidermis. The epithelium was the first tissue to regenerate, and it formed a thicker layer. Only the horny layer was thinner than in the control animal, possibly owing to excessive desquamation. In strongly rayed animals, only scattered traces of hairs remained. Hair follicles frequently were empty as though the hairs had fallen out. Later buds of epithelium formed new follicles. Many polymorphonuclear leukocytes infiltrated the connective tissue, but there were fewer lymphocytes. There was no increase in collagen bundles. A larger dose of raying was required to produce the same effects in the mouse's tail as in the skin of the abdomen. Raying of the ear caused a yellowish-brown discoloration, and the ear later became moist or covered with a small crust. After from three to four days, an ulcer appeared, but bleeding or pus did not occur. Healing was sluggish. Pauli emphasized the need of care in evaluating the changes seen, the element of infection of the ulcer requiring particular consideration.

There is some difficulty in estimating the voltage used by Pauli, but it did not exceed 50,000 in any of his experiments and was therefore always considerably less than the smallest voltage that we employed. On the other hand, his window was probably much thinner. He was able to demonstrate marked cytotoxic properties of the cathode rays, including bactericidal ability.

We have not used any amphibians in our work thus far. Pauli and his associates noted a change of color in the toad's skin from green to brown. Coolidge and Moore [2] encountered an extraordinary phenomenon

in the healing of a cathode-ray burn in the shaved ear of the rabbit. The normal hair was gray, but the new hair was white. The explanation of this is a problem in itself. However, melanin, the normal coloring matter of the skin, as found in melanotic tumors is not changed in color by long exposures, as long as five minutes at 200,000 volts not altering its appearance.

The epidermal changes in the toad are probably comparable with our results in the rat. The fact that Pauli did not produce acute collagen degeneration in the toad may be due to the fact that he used too low voltage. The only noteworthy observation in his experiments with the amputation tail stump of *Triton taeniatus* is retardation of the healing process.

The pictures Pauli obtained in the skin of the white mouse are much like those we secured in the white rat, allowing, of course, for a different voltage. The discoloration of the hair and the epidermal necrosis with foci somewhat resembling intracutaneous abscesses are apparently typical cathode-ray lesions. Ulceration in Pauli's mice was less constant, presumably because of the lower voltage used. Pauli did not obtain the hyaline swelling and coalescence of collagen fibers in the corium which were invariably present in our animals, although in a few instances he noted an increase in the size of the collagen bundles.

The fact that Wolbach found an acute hyaline degeneration of the collagen of the corium to be a characteristic roentgen-ray injury, and that we found the same lesion in our rats that were exposed to the cathode ray is in harmony with the generally accepted view that the physiologic effect of the roentgen rays is due to the cathode rays which they produce within the tissues.

The importance of a thorough study of the chronic effects of cathode-ray "burns" can be appreciated when we recall that chronic roentgen-ray dermatitis can lead to cancer of the skin. Small doses of roentgen rays are known to stimulate and larger doses to inhibit tissue repair. In therapeutics, a limited use has been made of this fact. Chronic roentgen-ray ulcers, it is well known, are slow to heal, and atypical epithelial changes may eventually occur, with the development of so-called precancerous roentgen-ray dermatoses, or later true carcinomas. Wolbach,[3] in his study of cancers in man caused by the roentgen ray, has indicated the probable histologic sequences in this neoplastic change.

Pauli [6] has shown that the cathode rays in small doses will stimulate healing of wounds. Our studies indicate that massive doses effectually depress epithelial regeneration. The long-standing effects of single and multiple exposures are being investigated in this laboratory and will be reported later.

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6. Pauli, W. E.: Die Bedeutung der Kathodenstrahlen fuer medicinische Fragen, Deutsche med. Wchnschr. **53**:133, 1927.

SUMMARY

A study was made of the biologic action of cathode rays on the skin of the white rat, the new Coolidge tube, a modification of the Lenard tube, being used. This tube permits observation of the effects of the cathode rays in the air outside the tube. The voltages used were 100,000, 200,000 and 350,000, and a current of 1 milliampere. An area about 2.5 cm. in diameter of the abdominal skin of the white rat was exposed to the cathode rays, at a distance of 2.5 cm. from the window of the tube. Thirty-six rats were used in these experiments, different groups being exposed to the rays, one tenth of a second and six seconds daily for fourteen days, and in single exposures of six, eight, ten, thirty and sixty seconds, respectively.

The intensity of the reaction of the skin varied according to the voltage and the length of exposure to the cathode rays.

During the actual raying, the animal would have a generalized muscular spasm, but otherwise did not show any systemic reaction, either during the exposure or afterward, except such reaction as might be attributed to absorption from the slough.

The macroscopic changes seen in this series of animals were, first, an immediate change in color of the white hair to yellow. When the hair had previously been removed, a pronounced redness and edema occurred. After forty-eight hours, the skin gradually became leathery and shrunken; it desquamated and an area of necrosis developed at the site of raying, the ulcer never extending in depth further than the first muscle layer. A thick crust formed, but healing was sluggish; in only one rat was epithelial repair far advanced after fourteen days.

The most characteristic lesion in the skin is a fusing of the collagen fibers of the corium and necrosis of the epithelium of the skin and hair follicles. Chemical changes produce marked alterations in the staining properties of the rayed tissues. Vascular injury is less severe and is most in evidence after the hyaline fusion of the collagen appears. Separation of the zone of necrotic skin and collagen is accomplished by the digestive action of leukocytes. Epithelial repair takes place from the periphery of the wound and at a slow rate.

The depth of penetration of the primary cathode rays as measured by the thickness of the zone of fused collagen in the photographs varied from 0.07 to 0.22 mm.; but, allowing for shrinkage of the tissue, the penetration is probably twice that depth.

As the cathode rays produce hyaline fusion of the collagen of the corium, and since the characteristic lesion of roentgen-ray injury is a similar collagen degeneration, the evidence seems conclusive that the biologic effects heretofore attributed to roentgen rays are not due to roentgen rays, but to the cathode rays which they produce in the tissues.

ANEURYSM OF THE RENAL ARTERY *

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In the literature dealing with the subject of aneurysms as applied to the renal artery and its main branches, the term has been generally used in a broad sense to include true and false, and perforated as well as nonperforated types. Unruptured aneurysms of the renal artery, which, as a rule, are found incidentally at postmortem examinations and are therefore of minor or no clinical interest, have received but little consideration. Rupture of the renal artery, associated with either a true or a false aneurysm, attended usually by prominent clinical manifestations and followed not infrequently by death, has occasioned the publication of a number of important pathologic as well as clinical studies.

The first case of aneurysm of the renal artery to appear in the literature, according to Vogeler,[1] was described by Nobel in 1719. Since that time Conroy [2] was able to collect thirty-one additional cases, not including the museum specimen in St. Bartholomew's Hospital which lacked the clinical history, or the case published by Vogeler in which operative or postmortem confirmation of the clinical diagnosis was lacking. Since the appearance of Conroy's article in 1923, six references to the subject are listed in the medical indexes under the title of "Aneurysm of the Renal Artery" (Roth,[3] Schramm,[4] Richardson,[5] Soderlund,[6] Healey [7] and Chisholm [8]), to which may be added two cases to be described here, bringing the total up to forty.

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* From the Departments of Medicine and Pathology of the University of Illinois College of Medicine.

1. Vogeler, K.: Das Nierenaneurysma, Deutsche Ztschr. f. Chir. **176**:297-324, 1922.

2. Conroy, M. J.: Aneurysm of the Renal Artery, Ann. Surg. **78**:628-640, 1923.

3. Roth, L. J.: Spontaneous Perirenal Hematoma, California State J. Med. **22**:54-56, 1924.

4. Schramm, H.: Aneurysm of the Renal Artery, Ann. Surg. **81**:105-107, 1925.

5. Richardson, C. B.: Aneurysm of a Branch of the Renal Artery, Brit. M. J. **1**:70-71, 1925.

6. Soderlund, G.: Calcified Aneurysm of Left Renal Artery, Acta chir Scandinav. **58**:649-665, 1925.

7. Healey, F. H.: Bilateral Renal Aneurysm, Brit. M. J. **1**:374, 1926.

8. Chisholm, A. E.: Rupture of Aneurysm on Branch of Left Renal Artery, Complicating Pregnancy, Brit. M. J. **1**:419-420, 1926.

When the accuracy of the statistics dealing with the subject of aneurysm of the renal artery is investigated one is impressed by the fact that the figures usually given for the incidence of aneurysm are far below the number of published reports. The wide discrepancy between the numbers collected and reported is explicable on the basis mainly of difference in classification. Variations in classification are due in turn to the option an author has for choosing for his title in addition to the names of the malady discussed its cause or its effect. The etiology and consequences of an aneurysm of the renal artery being frequently demonstrable, the condition may be logically classified in medical archives under any one of at least three heads, viz., the aneurysm itself, the disease process which led to its formation or the effect produced by its rupture (hemorrhage).

The tendency to classify conditions under the cause finds exemplification in that rare but interesting disease periarteritis nodosa. One does not find in the comprehensive reviews of renal aneurysm (Keen,[9] Morris,[10] Ziegler,[11] Trulli,[12] Vogeler,[1] Conroy [2] and Israel [13]) reference to saccular outpouching of the renal artery resulting from Kussmaul-Maier's disease. When the literature listed under the subject of periarteritis nodosa is consulted, however (Gruber [14]), it is found that aneurysm of the renal artery, either latent or manifest, is alluded to frequently.

In cases in which hemorrhage due to perforation of an aneurysm dominates the picture, the tendency often is to designate the report according to the effect produced, i. e., perirenal bleeding. A distinction in the literature is usually drawn between aneurysm of the renal artery and perirenal hematoma due to other causes (Israel,[13] Meyer and Singer [15]). Notwithstanding, one finds in reviewing the collected reports instances of unquestionable aneurysm listed as perirenal hematomas.

Another reason for the extreme paucity as indicated by collected statistics of aneurysm of the renal artery, besides the lack of uniformity in classification, is the frequent failure to include the symptom-free

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9. Keen, W. W.: Nephrectomy for a Large Aneurysm of the Right Renal Artery, etc., Philadelphia M. J. **5**:1038-1042, 1900.

10. Morris, H.: Aneurysm of the Renal Artery, Lancet **11**:1002-1010, 1900.

11. Ziegler, P.: Das Nierenaneurysma, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **6**:2-8, 1903.

12. Trulli, N.: Sugli aneurismi dell'arteria renale, Policlinico (sez. prat.) **23**:1223-1229, 1916.

13. Israel J.: Chirurgie der Niere und des Harnleiters, Leipzig, Georg Thieme, 1925.

14. Gruber, G. B.: Kasuistik und Kritik der Periarteritis Nodosa, Zentralbl. f. Herz. u. Gefässkrankh., 1926, vol. 18.

15. Meyer, K. A., and Singer, H. A.: Spontaneous Perirenal Hematoma, to be published.

group found at postmortem examinations. Vogeler,[1] in pointing out the rarity of the condition, states that in a total of 22,137 autopsies only four renal aneurysms were found. So far as could be ascertained, none of these cases was recorded in the literature under the appropriate title.

The following two cases are of particular interest from the standpoint of elucidation of the pathogenesis of aneurysm of the renal artery. It is especially noteworthy that in both instances microscopic studies were required to shed light on the nature of the respective underlying pathologic processes.

REPORT OF CASES

CASE 1.—*History.*—A white woman in the late fifties developed, without apparent cause, sudden pain in the right loin, followed by hematuria. Through cystoscopic examination it was learned that the origin of the blood was exclusively the right kidney. Not until recurrent attacks of pain and hematuria had reduced the patient to an anemic and asthenic state was surgical intervention permitted.

Operation.—At the operation the surgeon was unable to find the source of the hematuria, even after multiple incisions into the kidney substance. Nephrectomy was performed, and the extirpated kidney was delivered for examination to Dr. R. H. Jaffé who summarized the essential alterations.

Morbid Anatomy.—Grossly, the organ presented externally the characteristic changes of an arteriosclerotic contracted kidney. The renal artery and its main divisions were diffusely thickened. On broad section of the kidney and pelvis, there was seen at the lower pole projecting into and eroding the lining of a major calyx, a hematoma, which on careful dissection was found to be periarterial. The source of the hemorrhage was a ragged perforation in an interlobar artery just beyond its point of origin. The site of rupture corresponded in location to a deep red fusiform thickening of the vessel wall 4 mm. in length. The remainder of the renal vessels showed the usual changes of a rather marked atherosclerosis with disseminated plaques of intimal thickening.

The microscopic appearance of the ruptured artery was particularly noteworthy in that it depicted clearly the morbid processes which have led to the solution of continuity of its wall. Examination of a cross-section of the artery (fig. 1) showed a small interruption of its wall measuring 0.2 mm. (*a*) and an extravasation of blood from the lumen into the surrounding tissue (*b*). Using special stains, the elastica interna (*c*) was seen as a tortuous band in many places broken up and frayed to form several parallel thinner layers (*d*). Corresponding to the point of perforation of the artery the elastica interna was completely destroyed. The media (*e*) was in general, of twice the normal thickness and appeared irregular in structure, the smooth muscle bundles being cut in various planes and separated by a great deal of fibrillar connective tissue, the latter staining distinctly pink with the van Gieson technic. Few thin elastic fibers were found in this layer of the vessel wall. At the site where the elastica interna was absent, the media was thinned and, together with the elastica externa and adventitia, was destroyed, thereby permitting free communication of the lumen with the periarterial tissues. The elastica externa (*f*) consisted of many thin tortuous layers from which fibers passed into the adventitia (*g*). The latter was infiltrated by a large number of red blood cells which extended into the surrounding tissue.

Changes in the media which constituted the outstanding features in the foregoing picture were not limited to the ruptured vessel but could be found in sections taken from other portions of the kidney involving the smaller arteries also. The focal distribution of the damage to the media is illustrated in the accompanying photomicrograph of an arcuate artery (fig. 2). At one point (*a*) was seen localized thinning of the medial coat with extensive invasion and replacement of connective tissue, together with an infiltration of round cells into the adventitial layers. The decrease in the width of the vessel wall at the site of the lesion (*a*) could be best appreciated when a relatively normal area (*b*) was compared. Thickening of the intima (*c*) contrary to expectation was most marked at a distance from the zone of medial destruction.

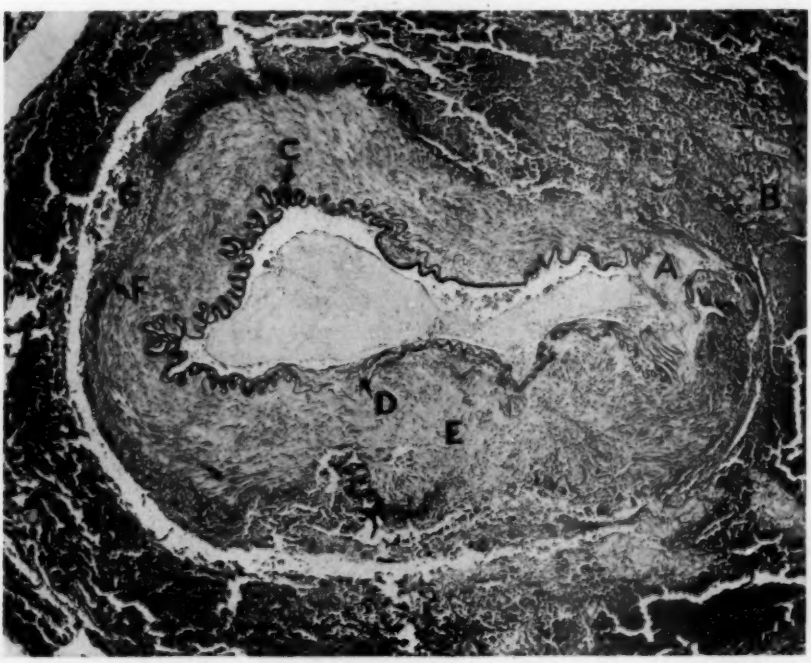

Fig. 1.—Ruptured interlobar artery of the kidney (elastica-van Gieson stain); the tear at *a* permits communication of the lumen with the periarterial tissues *b*; the internal elastic membrane *c* is frayed at *d*; the muscle bundles of the thickened media *e* are irregularly divided by connective tissue; some of the thin, tortuous fibers of the external elastic membrane *f* extend into the adventitia *g*; magnification 40 diameters.

The alterations in the vessels of the kidney other than those described do not need any particular comment as they represent the well known lesions of atherosclerosis. The changes in the parenchyma of the kidney were those of a moderate arteriosclerosis and arteriolosclerosis.

Comment.—The connective tissue replacement of the muscular elements which was particularly striking in sections stained with the van Gieson method gave one the impression that the medial damage was the most important factor in the genesis of the arterial rupture. This impression is of special interest owing to

the fact that little attention is accorded the media as compared with the intima in the study of vascular disease other than syphilitic conditions. On account of the meager history obtained and the lack of distinctiveness of the lesions it is not possible to explain the medial changes that occurred although it is presumed that they were the result of a previous infectious disease, probably nonsyphilitic.

CASE 2.—*History.*—M. H., a white woman, aged 46, was admitted to the medical service of Dr. William Quigley at the Cook County Hospital, Aug. 22, 1926, complaining of severe abdominal pain with persistent vomiting, of seven days' duration. Two previous similar attacks, neither as severe nor as prolonged,

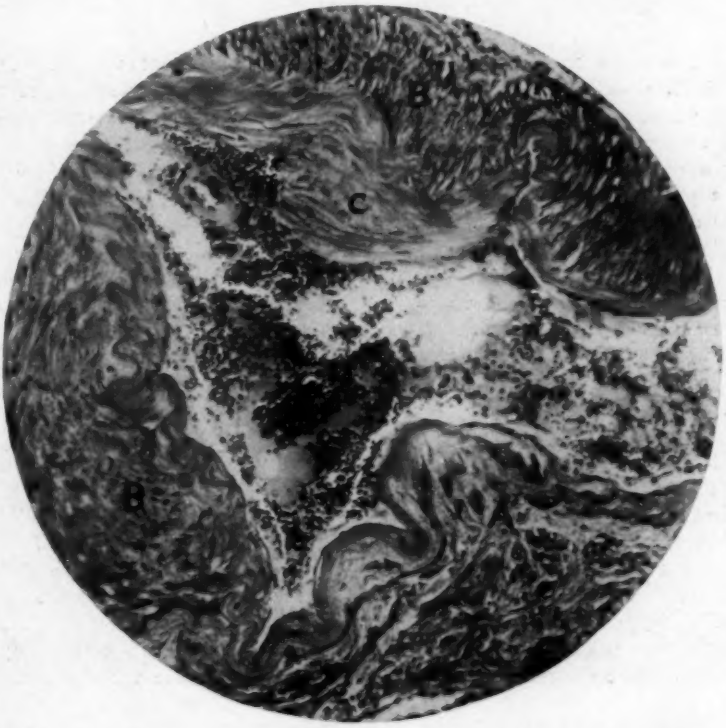

Fig. 2.—Cross-section of an arcuate artery; the medial coat is notably thinned at one point *a*, as compared with a normal area *b;* the intimal thickening *c* is most marked at a distance from the site of maximum damage to the media; magnification 120 diameters.

occurred during the two months preceding the patient's entrance into the hospital. A tumor mass located in the right side of the abdomen was palpated and thought to be of renal origin. The right abdominal mass increased so rapidly in size as to suggest the presence of a hemorrhage. Following cystoscopic examination, which showed that the outflow of urine was obstructed on the right and that the left kidney was functionally intact, the patient was submitted to operation, with a diagnosis of perirenal hematoma of unknown etiology. No history of trauma or any other information was elicited to suggest a possible basis for the hemorrhage. The operation performed by Dr. Karl A. Meyer

disclosed masses of freshly clotted blood about the convexity and lateral surfaces of the kidney. When the renal pedicle was exposed, there was encountered in the proximal portion of the anterior surface of the renal artery a perforation from which a jet of blood escaped with each cardiac pulsation. The bleeding vessel was clamped, and a nephrectomy was performed. On account of the proximity of the rupture to the point of origin of the renal artery, the possibility of dividing the artery proximal to the perforation was precluded. During convalescence, there was a profuse discharge of pus from the wound, smears of which contained many cocci in chains and clusters.

Pathologic Report.—Grossly the extirpated kidney did not present any noteworthy alteration except for the presence of dark red clotted blood covering its convex and lateral surfaces and grayish white somewhat firm tissue about its root. The renal capsule was intact throughout and except for the adherent clotted blood did not present any particular change. The renal parenchyma, except perhaps for a moderate degree of pallor, was likewise unaltered. In the renal artery and its main branches a few raised plaques were present but no other changes (it is to be remembered that the renal artery was divided distal to the point of perforation). At the lower pole the veins were occluded by recent adherent thrombi.

Microscopically, except for a patchy intimal thickening of slight degree, no remarkable changes were present in the main renal artery or its larger branches; nor were any noteworthy alterations found in the smaller arterial radicals or in the parenchyma of the kidney. In a number of sections taken from the firm, grayish tissue located in the hilum of the kidney the presence of a distinctly pathologic process was rendered apparent. The normal fatty areolar tissue was markedly altered owing mainly to diffuse cellular infiltration and proliferation, together with the presence of peculiar vascular elements. The changes in the peripelvic tissues were best illustrated along the outer edge of a representative section in which the fat had undergone marked atrophy, the cells being separated into small groups and isolated from each other by a loose, fibrillar connective tissue. The individual fat cells were shrunken and often appeared to be invaded by histiocytes. Within this area a marked infiltration of polymorphonuclear leukocytes, macrophages, round cells and plasma cells, associated with the development of fibroblasts and the dilatation of thin-walled blood vessels, was seen. The accumulations of inflammatory cells became less dense in passing centripetally, whereas the young connective tissue elements appeared more prominent and the vascular structures stood out in bold relief. As the opposite side of the section was approached, in a typical field (fig. 3), numerous vessels were seen separated by a loose tissue rich in fibroblasts, among which were scattered macrophages and round cells. Some of the vessels were represented by blood spaces lined by a single layer of endothelium (*a*), others had thicker walls which corresponded more or less to the caliber of the vessels (*b*), while still others presented disproportionately thickened walls (*c*). Involving the great majority of the vascular elements of the last mentioned group (*c*), a most striking change was observed. From a fraction to the entire circumference of many of the thickened vessel walls were found in a state of fibrinoid necrosis (*d*), for instead of consisting of well defined concentric layers of fibrillar tissue they were transformed into structureless and, except for degenerated remnants of nuclei, homogeneous masses which stained bright red with eosin.

Comment.—On the basis of the microscopic evidence, the presence of an inflammation involving the fat about the root of the kidney can be safely assumed to have existed. The relationship of the inflammatory process to the arterial rup-

ture is, however, somewhat conjectural. Drs. E. R. LeCount and R. H. Jaffé, both of whom examined the original sections, arrived independently at the conclusion that a low grade infection at the root of the kidney leading to erosion of the renal artery would best explain the changes found. Subsequent questioning of the patient elicited information highly suggestive of a previous retrocecal appendicitis.

Of particular interest in connection with the cases presented is the subject of etiology of renal aneurysm. For purposes of classification, the causes of aneurysm of the renal artery may be divided into traumatic and nontraumatic. The latter group can be further subdivided into

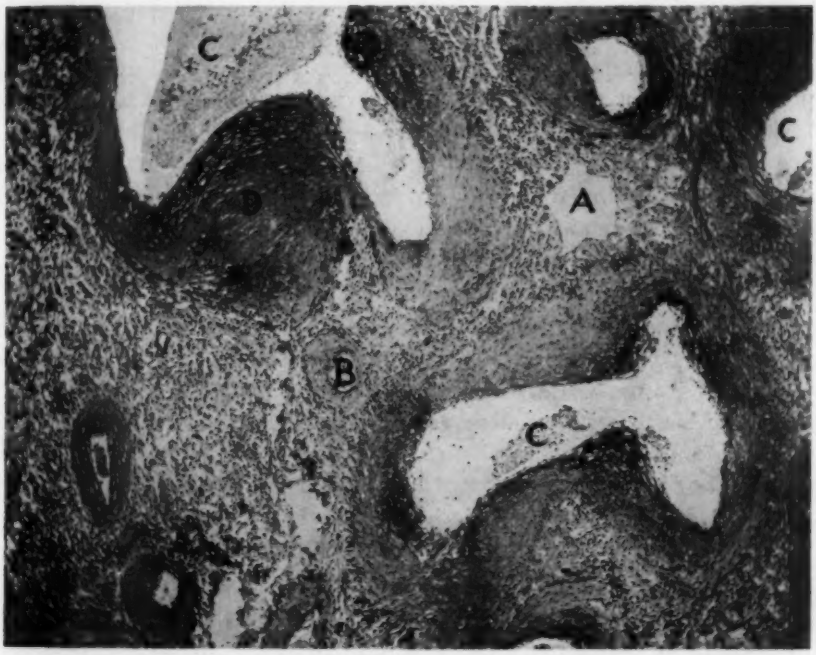

Fig. 3.—A section of the altered peripelvic fat of the hilum of the kidney; this highly vascularized tissue contains blood spaces lined by a single layer of endothelium *a* and vessels with proportionately *b* and disproportionately *c* thickened walls; the areas of fibrinoid necrosis *d* which stain bright red with eosin appear dark in the photographic reproduction; magnification 40 diameters.

primary disease of the arterial wall, either degenerative or inflammatory, and secondary disease due to extravascular morbid processes.

The rôle of trauma is the most important one in the causation of aneurysm of the renal artery, being the responsible agent in approximately 50 per cent of the reported cases. The nature of the injury which may be subcutaneous or perforating varies in degree of severity between wide limits. An insignificant trauma, as a sudden forceful

bodily movement, can act as a causa efficiens. It must be borne in mind, however, that injury to the pedicle of the kidney is infrequent, as compared with trauma to the renal tissue itself (LeCount [16]). In the nontraumatic group, primary disease of the vascular system assumes the leading position. A degenerative process (arteriosclerosis) is incriminated in 15 or 40 per cent of Conroy's collected cases in which the history of trauma was absent. Probably, some of the cases included in the traumatic group in which the injury was slight, such as a sudden twist, might better be classified among the arteriosclerotic group, since the fragility of the vessels involved appears to be the predisposing and more important factor. The changes in the renal artery, as a rule constitute but a part of a generalized vascular sclerosis, as in the case reported by Lincoln,[17] although the renal vessels may present the most advanced lesions. Aneurysms on an atherosclerotic basis may rarely be multiple, as in the case reported by Healey [7] in which one large and three smaller aneurysmal dilatations involved the right renal artery and similar but smaller sacculations occurred on the left. I have seen the same picture with, in addition, rupture of one of the aneurysms involving sclerotic vessels at the base of the brain. Among the conditions which produce inflammatory changes of the renal vessels, periarteritis nodosa, although itself rare, plays the leading rôle. This disease affects with predilection the medium sized vessels of the body and especially those of the kidney. In some cases the presence of an aneurysm is an accidental observation, but in others aneurysmal rupture may predominate the clinical picture and be the precipitating factor in the production of death (Mertens,[18] Harris and Friedrichs,[19] Laux,[20] Walter,[21] Müller [22]). Syphilis has also been incriminated as a cause of renal aneurysm. Bevacqua [23] describes a case of perirenal hematoma due to a gummatous arteritis of the renal vessels.

Extra-arterial disease can likewise be the basis of renal aneurysm. The occasional occurrence of aneurysm of the renal artery resulting

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16. LeCount, E. R.: Personal communication to the author.

17. Lincoln, W. A.: Spontaneous Rupture of the Renal Artery, J. A. M. A. **70**:80-82 (Jan. 12) 1918.

18. Mertens, E.: Ueber Periarteriitis nodosa mit Massenblutung ins Nierenlager, Klin. Wchnschr. **1**:1841-1843, 1922.

19. Harris, W. H., and Friedrichs, A. V.: Periarteritis Nodosa with a Classification of the Pathology, J. M. Research **43**:285-313, 1922.

20. Laux, F. J.: Periarteriitis nodosa, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **38**:582-591, 1925.

21. Walter, H.: Beiträge zur Histopathogenese der Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **25**:306-333, 1921.

22. Müller, H., cited by Gruber (footnote 14).

23. Bevacqua, A.: Sull' ematoma perirenale spontaneo, Policlinico (sez. chir.) **21**:592-600, 1924.

from thrombo-ulcerative endocarditis is illustrated in the case reported by Barnard.[24] It is to be assumed that septic processes other than endocarditis in which mycotic emboli are formed can similarly lead to miliary and larger aneurysms. Local, as well as distant, extra-arterial processes may act as etiologic factors. In the second case described, the changes found in microscopic preparations favor the view that a low grade inflammation about the kidney root led to localized erosion of a main renal artery and weakening at the affected site, with subsequent saccular dilatation and rupture. A unique case illustrating another type of extra-arterial erosion is reported by Janssen.[25] In this author's case the operative removal of a kidney stone by nephrotomy was followed seven days later by hemorrhage from the wound, the source of which was discovered through secondary operation and nephrectomy to be an aneurysm of a branch of the renal artery. The saccular dilatation was apparently produced by a sharp corner of the stone which eroded the vessel, the rupture, presumably, following relief of the counter-pressure exerted hitherto by the stone.

SUMMARY

Aneurysm of the renal artery is not rare. Its apparent infrequency, as judged by statistical reports, is explained by the lack of uniformity in classification.

Two cases of aneurysm of the renal artery are recorded, in each of which the genesis of the underlying pathologic process was brought to light by histologic studies. In the first instance, the primary lesion apparently was a degenerative change of nonspecific character, involving the media and causing a weakening of the vessel wall. The evidence in the second case favored the assumption that the renal artery was eroded by an inflammation which had its seat in the fat at the hilum of the kidney.

The causes of the condition can be divided into traumatic and non-traumatic. The latter group includes primary disease of the arterial wall, either degenerative or inflammatory, and secondary disease due to extravascular morbid processes.

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24. Barnard, H. C.: A Calcified and Cured Aneurysm of the Right Renal Artery in a Boy, Tr. Path. Soc. London **52**:254, 1900-1901.

25. Janssen, P.: Zur Klinik der intrarenalen Aneurismen, Ztschr. f. urol. Chir. **10**:130, 1922.

SACROCOCCYGEAL CHORDOBLASTOMA

REPORT OF A CASE

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The notochord develops from the fused mass of cells at the junction of the entoderm and the mesoderm of the primitive axis, forming a cordlike structure joining the mesodermal masses on each side. It extends from a point just caudal to the hypophysis to the caudal extremity of the embryonic body. In man it is merely a transient structure which disappears early in fetal life, leaving only slight traces in the centers of the intervertebral disks (Kolliker [1]), along the clivus blumenbachii and in the sacrococcygeal region. In a series of carefully conducted autopsies, Ribbert [2] found notochordal remnants in about 2 per cent of his cases; these were in the bony tissue beneath the clivus blumenbachii and perforated the dura around the basilar artery.

The notochordal cells are at first of an epithelial nature; those within the vertebral bodies become vacuolated, break up and disappear, leaving only the segments within the intervertebral disks. Later, these segments also undergo degenerative changes but persist in the so-called pulpy nuclei (Ribbert [3]).

These rudimentary cells of the chordo dorsalis may give rise to peculiar tumors having the character of embryonic entodermal tissue composed of groups of large vacuolated cells lying in a soft homogenous basic staining matrix. Macroscopically, the growth resembles a colloid carcinoma, with nodular areas of mucinoid substance held together by bands of fibrous tissue.

The cells at first have large distinct nuclei, which gradually become indistinct as the cells enlarge; the protoplasm becomes more granular and vacuoles filled with mucin develop. The cells may rupture and may discharge the mucin; they become shrunken, and the nuclei that remain resemble deeply stained masses of syncytial cells.

These growths are relatively benign as far as metastatic recurrences are concerned, but generally become locally malignant and invade and destroy all contiguous structures.

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1. Kolliker: Gewebelehre **1**:301, 1889.
2. Ribbert, H.: Geschwulstlehre, 1894, p. 149; Centralbl. f. allg. Pathol. u. path. Anat. **5**:457, 1912.
3. Ribbert, H.: Allg. Path. u. path. Anat., 1908, p. 241.

The first recorded case of chordoma was described by Luschka [4] in 1857, the growth being in the region of the sphenoid. In 1857, Virchow [5] described what he called ecchondrosis physaliphora on account of the belief that this tissue was an altered cartilageous structure with hydropic degeneration of the cells of the matrix. The tumor he described was also located in the region of the spheno-occipital synchondrosis.

The true nature of these growths was first mentioned by Muller [6] in 1858. He called attention to the notochordal remnants in the spheno-occipital juncture, the basilar cartilage and in the sacrococcygeal region and suggested that these growths were caused by the persisting masses of cells.

In 1889, Klebs [7] described a tumor of this nature which occurred in front of the upper cervical vertebrae.

Following these reports by Kolliker, Muller, Ribbert and Klebs, cases were reported by Henning [8] (a sacral chordoma in a 7 months' fetus), Grahl [9] (a lobulated extradural tumor involving the sella turcica), Hassner [10] (a spheno-occipital chordoma which had persisted and had caused pressure symptoms for four years before death, the tumor measuring 5.5 by 6.5 cm.), Fischer [11] (a malignant chordoma beneath the clivus blumenbachii, invading the spinal canal and compressing the cord) and Linck [12] (a tumor presenting in the pharyngeal vault, involving and compressing the cranial nerves arising near the clivus).

Other malignant and benign chordomas have been described by Feldman,[13] Vecchi,[14] Frenkel and Bassai,[15] Mazzia [16] and Albert.[17] These were all sacrococcygeal growths.

In 1912, Jelliffe and Larkin [18] described a large tumor on the clivus blumenbachii, growing into and infiltrating the substance of the brain. In 1913, Wood [19] described another sacrococcygeal chordoma.

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4. Luschka, H.: Virchows Arch. f. path. Anat. **11**:8, 1857.
5. Virchow, R.: Unter über die Ent. des Schadelgrundes, Arch. Berlin, 1858.
6. Muller: Ztschr. f. rat. Med. 1858, p. 202.
7. Klebs: Handb. d. allg. Path. **2**:693, 1889.
8. Henning, L.: Beitr. z. path. Anat. u. z. allg. Path. **28**:593, 1900.
9. Grahl: Inaug. Diss., Gottingen, 1903, cited by Fischer; Beitr. z. path. Anat. u. z. allg. Pathol. **40**:109, 1907.
10. Hassner: Virchows Arch. f. path. Anat. **99**:575, 1913.
11. Fischer: Beitr. z. path. Anat. u. z. allg. Pathol. **40**:109, 1907.
12. Linck: Beitr. z. path. Anat. **46**:573, 1909.
13. Feldman: Beitr. z. path. Anat. **48**:630, 1910.
14. Vecchi: Arch. f. klin. Chir. **99**:575, 1912.
15. Frenkel and Bassai: Arch. de med. exper. **22**:703, 1910.
16. Mazzia, O.: Centralbl. f. allg. Pathol. u. path. Anat. **21**:769, 1910.
17. Albert, H.: Surg. Gynec. Obst. **31**:766, 1915.
18. Jelliffe and Larkin: J. Nerv. & Ment. Dis. **39**:1, 1912.
19. Wood: Proc. New York Path. Soc. **13**:103, 1913.

Fig. 1.—Embryonic masses of syncytial cells arranged in pseudoalveolar formation by the proliferating inflammatory fibrous connective tissue stroma. Reduced from a photomicrograph with a magnification of 125 diameters.

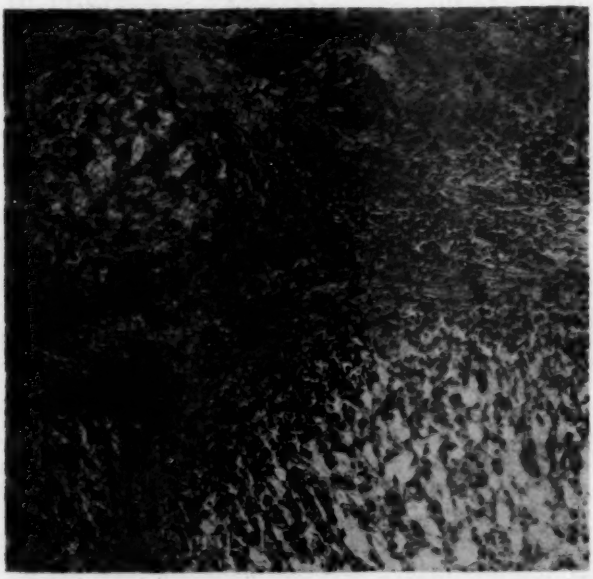

Fig. 2.—Physaliphore cells and masses of syncytial cells in pseudoalveolar formation. The connective tissue shows a dense infiltration by inflammatory cells. Reduced from a photomicrograph with a magnification of 125 diameters.

In 1922, Stewart [20] collected reports of twenty-six cases from the literature, fifteen occurring in the region of the spheno-occipital synchondrosis, nine in the sacrococcygeal region and two in other areas along the spinal structures. Stewart added a report of a sacrococcygeal growth that recurred after operative removal and that produced metastasis. Lemke [21] reported a chordoma in the region of the clivus blumenbachii, with extensive destruction of the basilar tissues. The tumor he described was of an extremely malignant form. Berard, Dunet and Peyron [22] described a malignant sacrococcygeal chordoma.

Fig. 3.—A portion of the tumor resembling embryonic masses of epithelial cells recalling the entodermal origin of this tissue. Reduced from a photomicrograph with a magnification of 125 diameters.

In 1923, Hirsch and Ingals [23] described a sacrococcygeal chordoma measuring 9 by 9 by 3.5 cm. The growth was nodular, grayish white, firm and painless. It was removed under local anesthesia. The histologic appearance was typically that of a chordoma; the growth was well encapsulated and apparently did not involve the bony structures. This is unusual, as the occurrence of such a growth in the soft tissues outside

20. Stewart, M. J.: J. Path. & Bacteriol. **25**:40, 1922.

21. Lemke, R.: Virchows Arch. f. path. Anat. **238**:310, 1922.

22. Berard, Dunet and Peyron: Abstr. in Centralbl. f. allg. Pathol. u. path. Anat. **33**:194, 1922.

23. Hirsch, E. F., and Ingals, M.: Sacroccygeal Chordoma, J. A. M. A. **80**:1369 (May 12) 1923.

the sacrum and without involvement of the bones has not been previously mentioned.

I wish to add a case of extensive malignant chordoblastoma involving the sacrum and coccyx and extending into the iliac bones and neighboring tissues of the buttocks.

REPORT OF CASE

A woman had suffered from a fall about five years previously and had complained of pain in the sacrococcygeal region for which she had consulted numerous physicians without relief.

Fig. 4.—An area of the tumor showing physaliphore cells. These large, clear cells are filled with mucin; some show vacuolization; others are collapsed because of the escape of the mucin content. Reduced from a photomicrograph with a magnification of 250 diameters.

In 1922, at 66 years of age, she first noticed a small swelling at the end of the spine which was about the size of the end of her index finger; it was tender, painful and soft. The swelling remained about the same size but became hard and less tender, although pain persisted. The swelling was incised, without relief. She came under observation on the service of Dr. William Fisher at St. Vincent's Hospital in March, 1923. Examination showed nothing else of importance considering the age of the patient; the growth was about 1.5 cm. in diameter and was elevated about 1 cm.; it was dusky red, hard, indurated and apparently deeply attached to the sacrum. The growth was not particularly tender, although the patient complained of constant pain in this region.

Under a local anesthetic, an incision was made over the sacrum, and it was seen that a soft, spongy, gelatinoid mass involved the sacrum; the coccyx was separated from the sacrum by the growth and was also involved. The coccyx was removed, and the soft tissues of the tumor curretted away; the wound was then

packed. This wound never healed, but continued slowly to become more extensive and required frequent current curettements and constant dressings.

In January, 1926, the area involved after three years, was about 7 inches (17.7 cm.) across by 5 inches (12.7 cm.) along the spine, and resembled a deep ulceration filled with gelatinoid, dusky red substance and containing spicules of necrotic bone. The surrounding skin was a dusky red for an area of about 2½ inches (6.2 cm.). The patient required constant care and suffered considerable pain and discomfort until her death in January, 1927, when she was 71. Death was caused by hypostatic pneumonia following debility from cardiovascular renal disease and the malignant chordoblastoma.

The pathologic examination of the tissue removed showed extensive destruction of bone by a soft, spongy tumor resembling bone marrow and connective tissue, with nodular areas of a clear, mucin-like substance.

Fig. 5.—Formation of masses of syncytial cells by the collapsing physaliphore cells. Reduced from a photomicrograph with a magnification of 250 diameters.

Microscopically, the tissue showed masses and strands of cells that were irregular in size and shape; many were vacuolated and contained a homogeneous gelatinoid substance. These were the so-called physaliphora cells containing mucin; they became shrunken from escape of the mucin, leaving multinuclear dark staining protoplasmic masses resembling masses of syncytial cells. A fine fibrillar connective tissue framework varying in density surrounded these large clear cell masses and formed pseudo-alveoli. Some areas showed degenerative changes in the center of the masses of cells that formed small cysts. The connective tissue showed considerable inflammatory cellular infiltration, and some interstitial hemorrhage was present. Areas of bone showing extensive absorption were seen in the growth. The diagnosis was sacrococcygeal chordoblastoma (malignant chordoma). The diagnosis was confirmed by Dr. James Ewing of Cornell University, New York, who examined a slide from the growth.

COMMENT

Chordoblastomas vary as to their benign and malignant characteristics, according to the location and the structures involved. They are all potentially malignant as far as recurrences are concerned but rarely produce metastasis. The number of cases observed shows that more frequent consideration must be given to the possibility of a tumor of this nature in cases presenting swellings or ulcerations in regions in which notochordal remnants may be present.

SUMMARY

A case of malignant sacrococcygeal chordoblastoma developing in a woman, aged 66, is reported. Death resulted after five years, during which extensive ulceration took place.

VITAMIN A DEFICIENCY IN THE GUINEA-PIG*

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AND
PERCY R. HOWE, M.D.
BOSTON

In man[1] and in the albino rat[2] a specific effect of vitamin A deficiency is found in epithelial structures and results in the substitution of stratified keratinizing epithelium for normal epithelium in the respiratory tract, alimentary tract, eyes, parocular glands and genito-urinary tract.

The demonstration of a similar pathologic process in a strictly herbiverous animal, the guinea-pig, supports the idea that the epithelial change is the expression of a fundamental physiologic requirement amenable to study. Publications on vitamin A deficiency in animals other than the rat are few and are meager in detail.

The nearest approach to feeding purified foods to species other than rats in the study of vitamin A deficiency was made by Nelson and Lamb.[3] They fed rabbits a synthetic diet, to which was added alfalfa which had been extracted with alcohol. Ophthalmia curable by supplying the deficient factor resulted.

That vitamin A is indispensable for dogs was demonstrated by Steenbock, Nelson and Hart[4] by the production of a pronounced ophthalmia curable by restoration of the diet. These authors remarked that the specific effect of lack of fat-soluble A in other species than the rat is generally arrived at by analogy.

Beach[5] reported the effects of vitamin A deficiency in fowls as follows: (1) nasal discharge, (2) ophthalmia, (3) lesions of the mucosa of mouth, pharynx and esophagus and (4) emaciation and weakness.

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1. Wilson, J. R., and DuBois, R. O.: Keratomalacia in Infant with Post-mortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923.

2. Wolbach, L. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, J. Exper. Med. **43**:753, 1925.

3. Nelson, V. E., and Lamb, A. R.: The Effect of Vitamin Deficiency on Various Species of Animals, the Production of Xerophthalmia in the Rabbit, Am. J. Physiol. **51**:530, 1920.

4. Steenbock, H.; Nelson, E. M., and Hart, E. B.: IX. The Incidence of an Ophthalmia Reached in Dogs Fed on Fat Soluble Vitamin Deficient Diet, Am. J. Physiol. **58**:14, 1921.

5. Beach, J. R.: Vitamin A Deficiency in Poultry, Science **58**:542, 1923.

Fig. 1 (guinea-pig 23).—Uterus; × 1.5. The animal was fed on a deficient diet for 105 days. At the beginning of the experiment it was 127 days of age and weighed 597 Gm. The maximum weight was 621 Gm.; the final weight, 480 Gm.

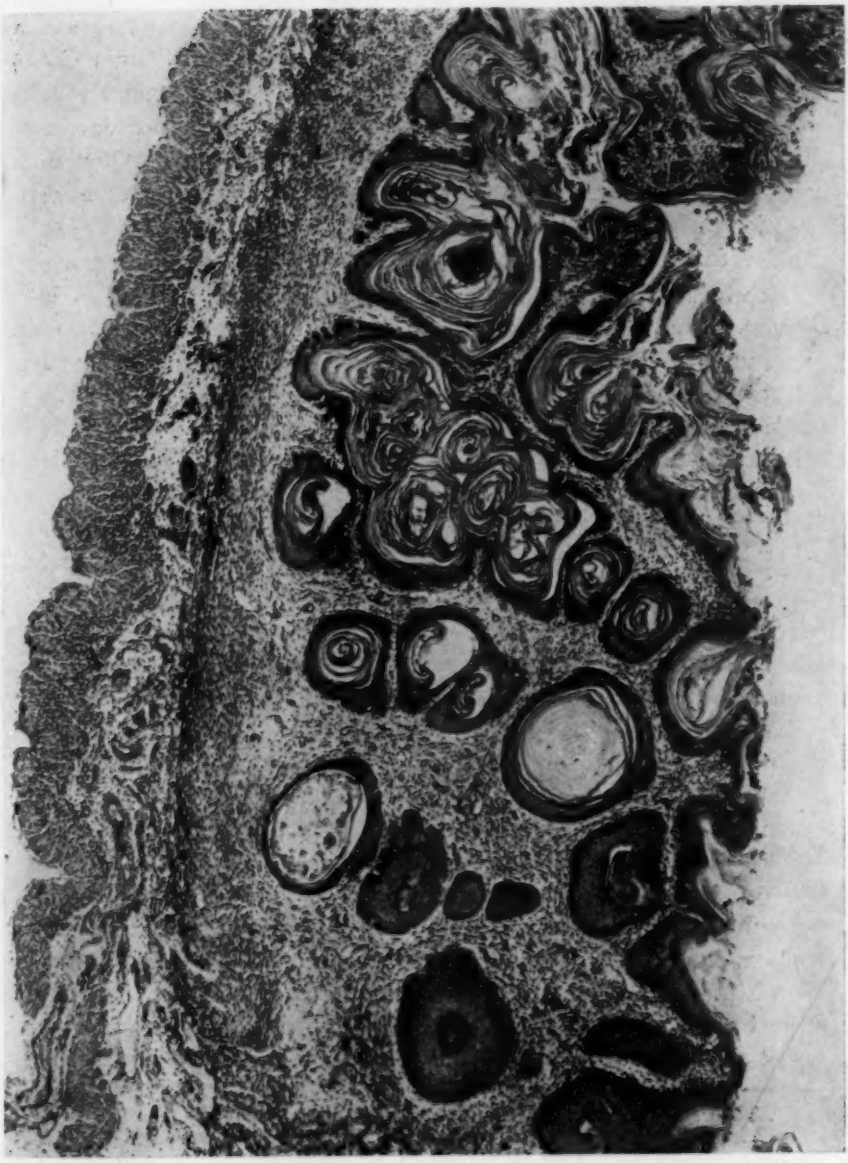

Fig. 2 (guinea-pig 23).—Section through the body of the uterus showing keratinizing epithelium and cyst formation; × 44.

Studies of vitamin A deficiency in guinea-pigs have been published by Tozer and by Boock and Trevan. Tozer [6] studied the effects of deficient diets on the costochondral junctions. The diet consisted of bran and oats as desired, with orange juice to supply vitamin C and milk autoclaved at 120 C. for an hour, to supply vitamin A. The guinea-pigs fed on the diet of bran, oats and orange juice developed changes in the costochondral junctions which Tozer interpreted as indistinguishable from those of chronic scorbutus. Almost immediate cessation of growth followed the withdrawal of milk in the diet as compared with the effects of the withdrawal of orange juice.

Boock and Trevan [7] attempted to use purified diets such as have been used on rats, but stated that their experiments were "brought to an untimely conclusion by the fact that the guinea-pigs refused to eat any of the deficient diet." By using a diet of natural foods and partially purified foods, they obtained effects attributable to vitamin A deficiency—cessation of growth and loss of weight, and in one guinea-pig, a cloudiness of the cornea. These effects were promptly ameliorated by the administration of cod liver oil.

Histologic studies were not made in any of the foregoing researches, with the exception of the costochondral studies by Tozer.

Our studies on vitamin A deficiency in guinea-pigs were undertaken as a natural sequence to our studies with rats and because they seemed desirable in the steps toward the establishment of a specific pathologic process irrespective of species. The difficulty attending the use of a purified diet encountered by Boock and Trevan was overcome by placing guinea-pigs from 4 to 6 weeks of age on the control ration of purified materials: casein, 15; starch, 74; butter fat, 6; Mendel's salt mixture, 3,[8] and yeast, 2. Guinea-pigs were selected that could be accustomed to take it. Filter paper and distilled water were given as desired. Measured amounts of orange juice, 20 cc. daily, from a dropper were given to prevent scorbutus.[9] The guinea-pigs were kept on this diet for a period of about four weeks and showed normal gains in weight. After we were assured that the guinea-pigs would eat the food readily and were constantly gaining in weight, the

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6. Tozer, F. M.: The Effect on the Guinea-Pig of Deprivation of Vitamin A and of the Anti-Scorbutic Factor; with Special Reference to the Conditions of the Costochondral Junctions of the Ribs, J. Path. & Bact. **24**:306, 1921.

7. Boock, E., and Trevan, J.: The Food Value of Mangolds and the Effects of Deficiency of Vitamin A on Guinea-Pigs, J. Biochem. **16**:780, 1922.

8. Osborne and Mendel's salt mixture, J. Biol. Chem. **32**:317, 1917.

9. All credit for success was due to the painstaking care bestowed on each guinea-pig by Miss Ruth E. Hatch of the Forsyth Infirmary.

Fig. 3 (guinea-pig 23).—Longitudinal section through the distal third of the cornu of the uterus showing the complete replacement of the epithelium by keratinizing epithelium with excessive growth; × 44.

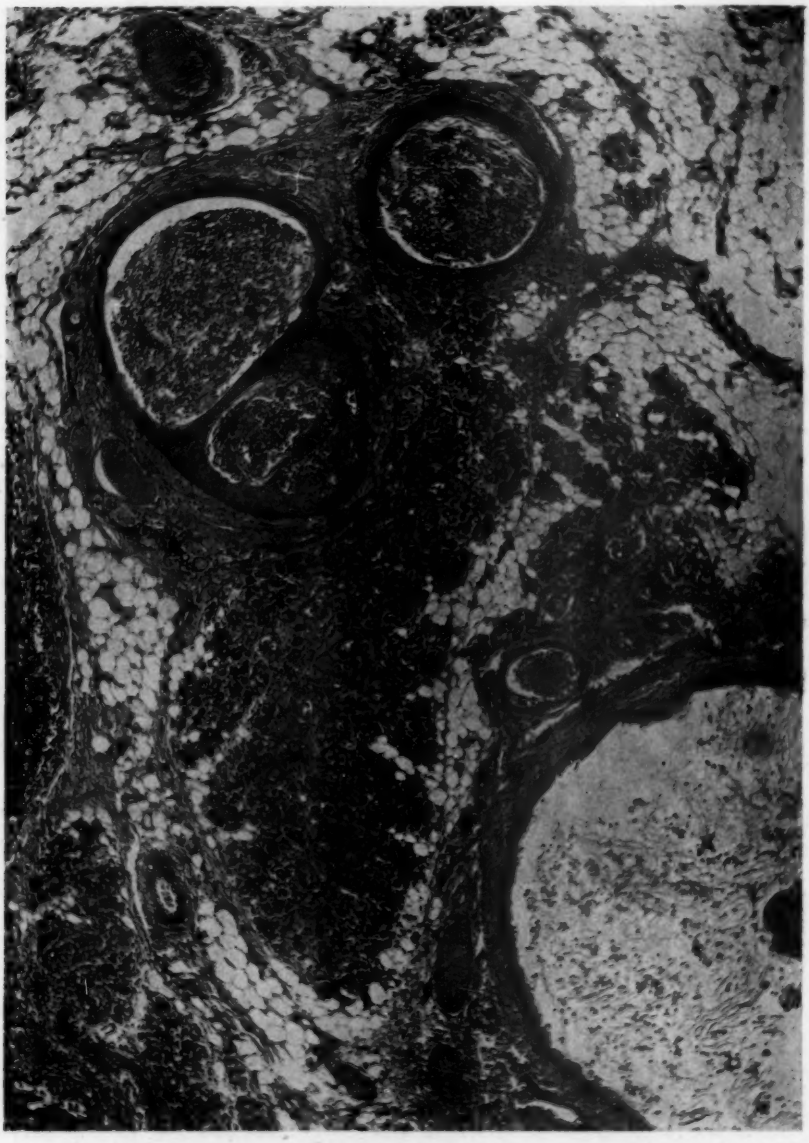

Fig. 4 (guinea-pig 26)).—Section of the submaxillary gland showing cysts produced by growth of keratnizing epithelium in the ducts; ×65. The animal was fed on the experimental diet for 105 days. At the beginning of the experiment it was 88 days of age and weighed 582 Gm. The maximum weight was 694 Gm.; the final weight, 471 Gm.

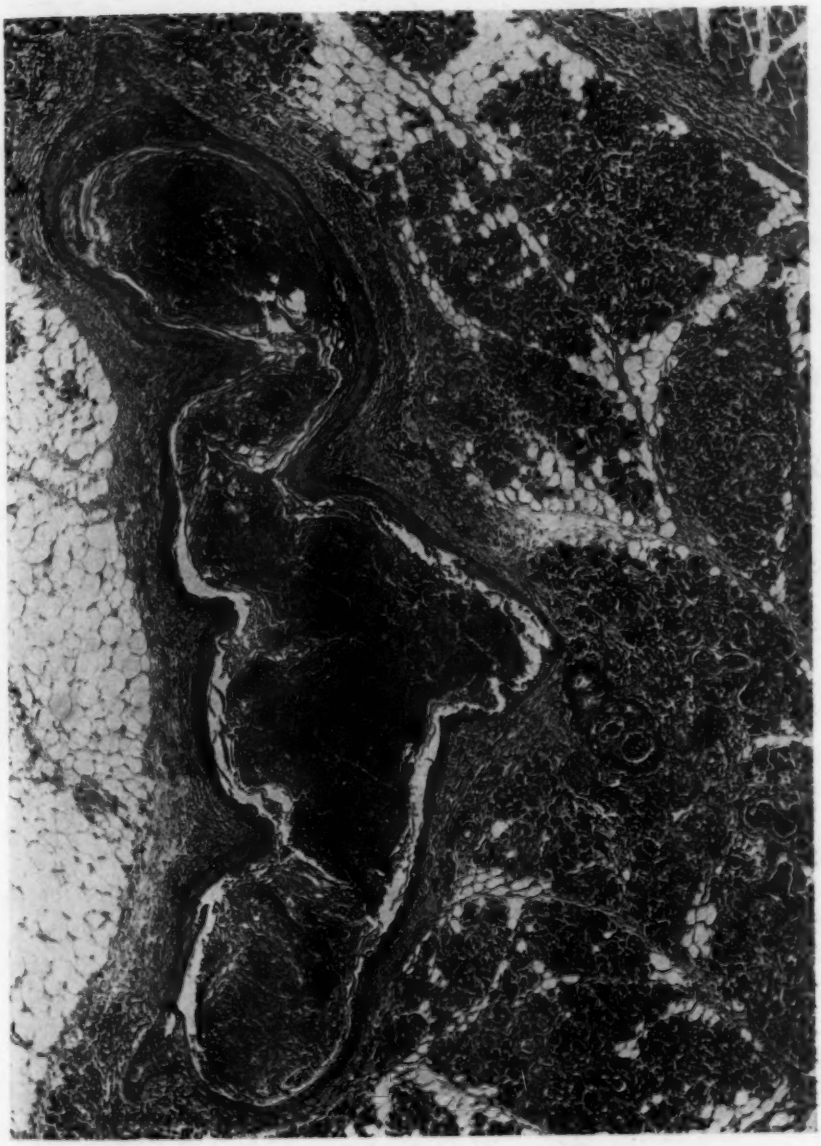

Fig. 5 (guinea-pig 26).—Section of the submaxillary gland.

deficient diet was substituted and the orange juice was gradually reduced in amount to about 4 cc. daily, a quantity which we found sufficient to prevent scorbutus.[10]

The deficient diet has the foregoing formula with lard substituted for butter. Weight curves and postmortem observations showed that the amounts of orange juice given contained a negligible amount of vitamin A for guinea-pigs. Each guinea-pig was kept in an individual cage in a well lighted and ventilated room. The cages and utensils were kept scrupulously clean, and the food rations and orange juice were given by hand.

During the preliminary period on the control diet, the guinea-pigs gained from an average weight of 350 Gm. to weights of 550 Gm. to 560 Gm. After they were placed on the deficient diet, the gain in weight progressed at the same rate for periods of from four to six weeks and reached an average maximum of 660 Gm., then an abrupt cessation of growth followed and a decline in weight which became more rapid in the second month of the experiments. The duration of life was from sixty-six to 110 days. In a few instances, there was a gain in weight due to edema before the animal became too weak to continue the experiment.

Guinea-pigs of 350 Gm. average weight gained steadily on the control diet over a period of thirteen months, reaching weights averaging 820 Gm. When they were killed, lesions were not found. Twenty-six guinea-pigs were maintained on the deficient diet for periods of from sixty-six to 110 days, in each instance, until it seemed no longer possible to keep the animal alive. Thirteen of these chloroformed were studied histologically.

The only external signs of vitamin A deficiency were cessation of growth and loss of weight. Lesions of the eye such as are the rule in rats did not occur. We had no instance of corneal opacity as described by Boock and Trevan in one of their guinea-pigs. Desiccation of the margins of the ears (pinnae) followed by a line of demarcation and separation of a narrow zone averaging about a millimeter in width occurred in most of the experimental series. The histologic events leading to this necrosis have not been fully worked out. Localized edema and epidermal proliferation are two early changes thus far determined. A considerable degree of edema of the omentum and retroperitoneal tissues was found in three guinea-pigs at postmortem examination; one of these animals had a striking edema of the subcutaneous tissues as well. The three guinea-pigs had been subjected to

10. Orange juice contains vitamin A as is noted in the literature and as we have ascertained in experiments with rats; 2 cc. daily having effected cures within twelve days in rats with xerophthalmia due to vitamin A deficiency.

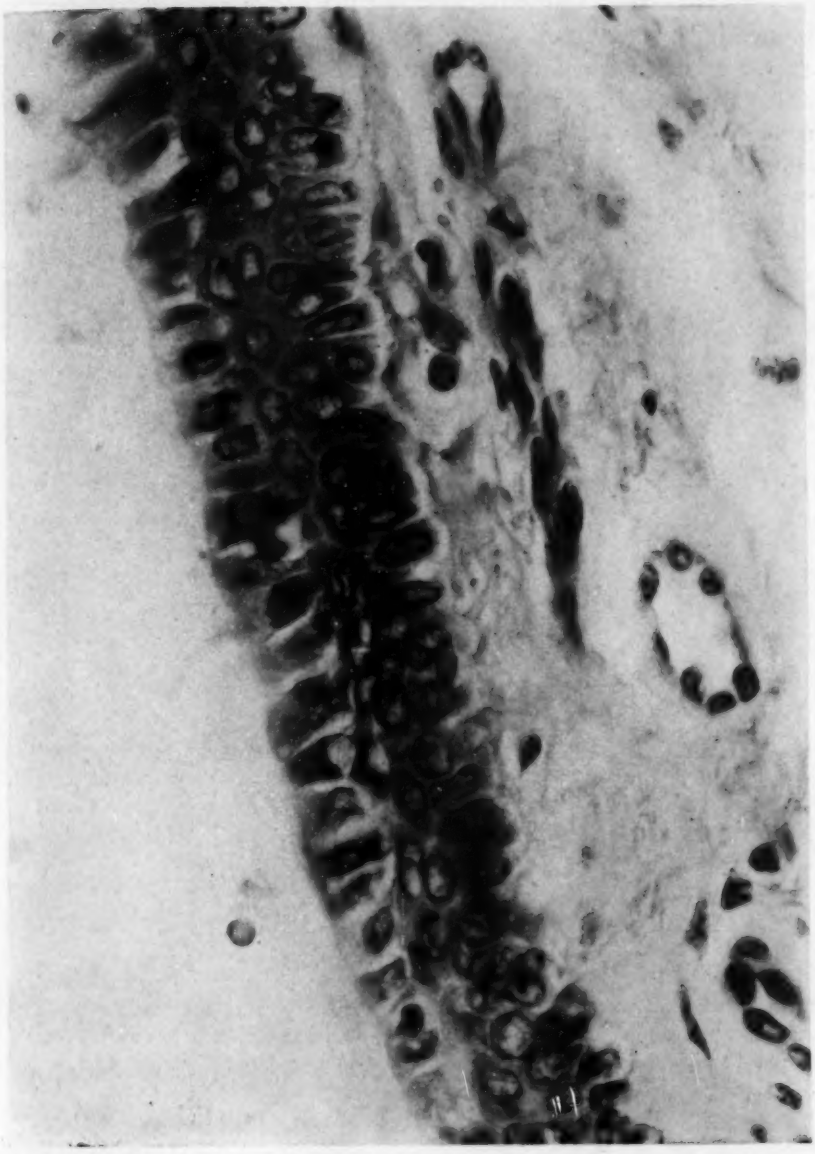

Fig. 6 (guinea-pig 11).—Section of the trachea showing the undermining of the original epithelium by the stratified keratinizing type; × 850. The animal was fed on experimental diet for 76 days. At the beginning of the experiment it was 79 days of age and weighed 499 Gm. The maximum weight was 616 Gm.; the final weight, 391 Gm.

random experimentation in the variation of amounts of orange juice administered, and the edema followed the giving of large amounts of orange juice after a period of almost complete deprivation.

Other postmortem observations were emaciation, atrophy of the salivary glands and the testes, and the effects of extensive keratinization of the epithelium in the trachea, bronchi, bladder and uterus. In striking contrast to the albino rat, our guinea-pigs frequently showed considerable amounts of subcutaneous and intra-abdominal fat with advanced

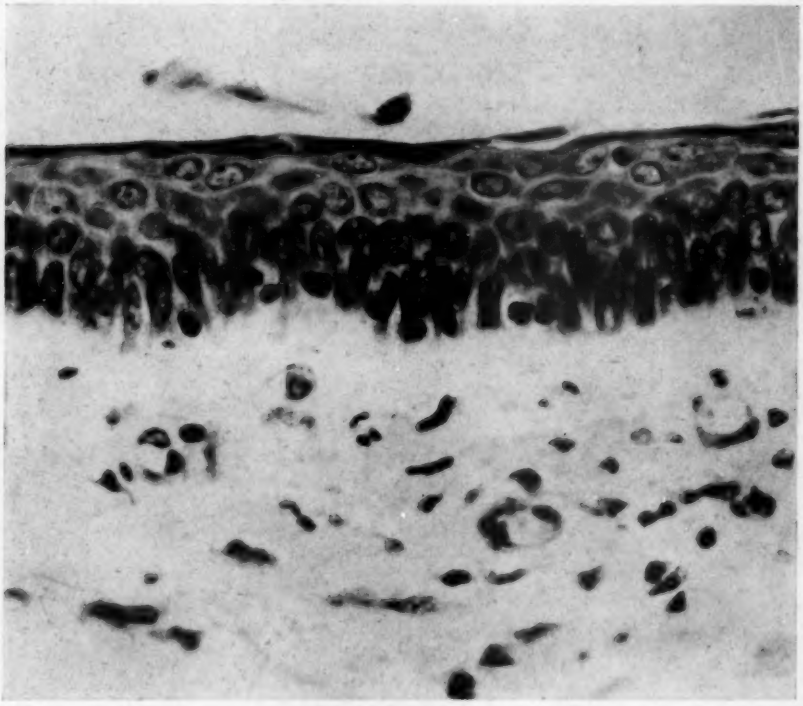

Fig. 7 (guinea-pig 15).—Section of the trachea showing the complete replacement by stratified keratinizing epithelium; × 700. The animal was fed 110 days on the experimental diet. At the beginning of the experiment it was 122 days of age and weighed 561 Gm. The maximum weight was 611 Gm.; the final weight, 347 Gm.

epithelial changes possibly indicative of a lower fat storage of vitamin A than in the rat.

The gross changes in the lungs were emphysema and bronchiectases due to the mechanical effects of desquamated keratinized cells in the bronchi and in the trachea. Small whitish and yellowish nodules were found occasionally in the salivary glands, these nodules proved to be cavities lined with stratified epithelium and filled with desquamated

keratinized cells. In three instances, the bladder contained pasty masses of keratinized cells, and the walls were strikingly thicker than normal with shaggy mucous membranes. In male guinea-pigs, there were often large accumulations of pasty material in the prepuce, and in two instances the seminal vesicles were opaque yellow and distended with cheesy material composed of desquamated keratinized cells. In the female guinea-pigs, the vagina invariably contained accumulations of

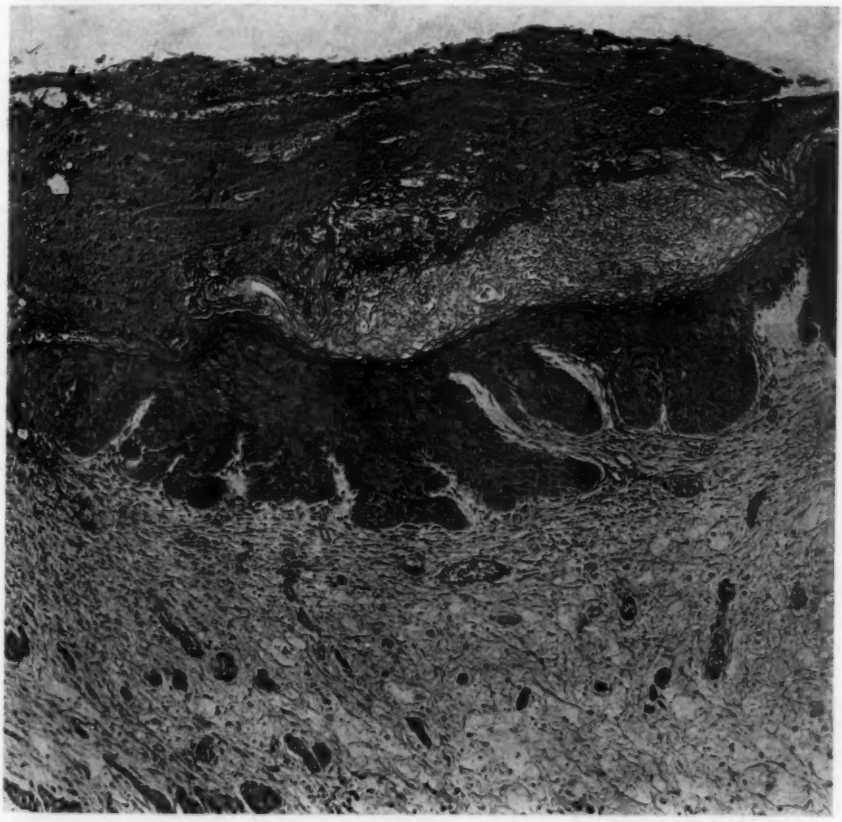

Fig. 8 (guinea-pig 26)).—Section of the bladder showing the excessive growth of keratinizing epithelium; × 65.

keratinized cells, and frequently the epithelium was thickened and shaggy. In five of six, the uterus presented striking enlargement and vascular injections (fig. 1). The walls were thickened in three instances, and both horns were distended with white pasty material. After the adherent debris had been removed, the mucosa was opaque white and shaggy. Cross-sections showed that the abnormal thickness of the walls of the uterus was due to an increase in the thickness of the

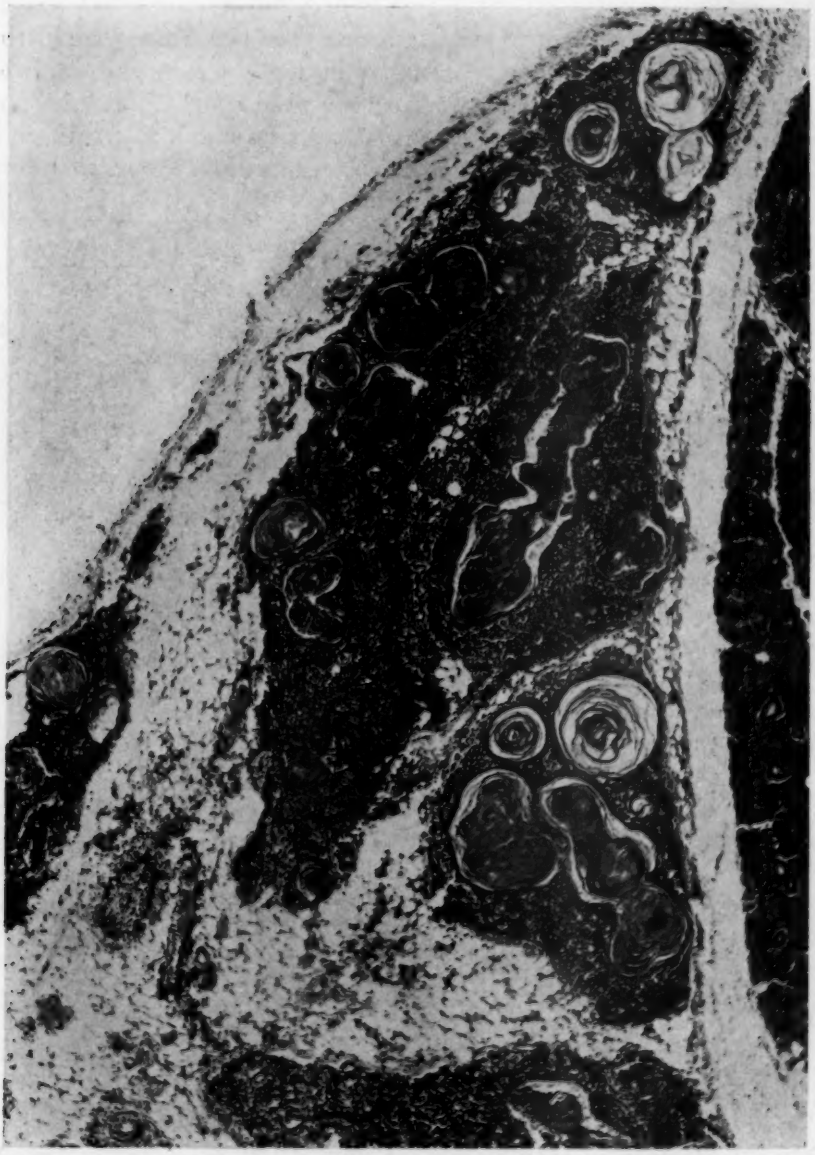

Fig. 9 (guinea-pig 28).—Section of the thymus showing atrophy and behavior of Hassal's corpuscles; ×65. The animal was fed on the experimental diet for 67 days. At the beginning of the experiment it was 130 days of age and weighed 510 Gm. The maximum weight was 599 Gm.; the final weight, 394 Gm.

mucosa. These changes involved the whole uterus, from the common os to the extreme tips of the cornua.

A microscopic description of the tissues of the guinea-pigs would practically duplicate the account we have given of the tissues of the rat in a previous publication.[2] The adequacy of the amounts of orange juice given was proved histologically, as a routine measure, by the absence of lesions in costochondral junctions. The liver, kidneys, para-

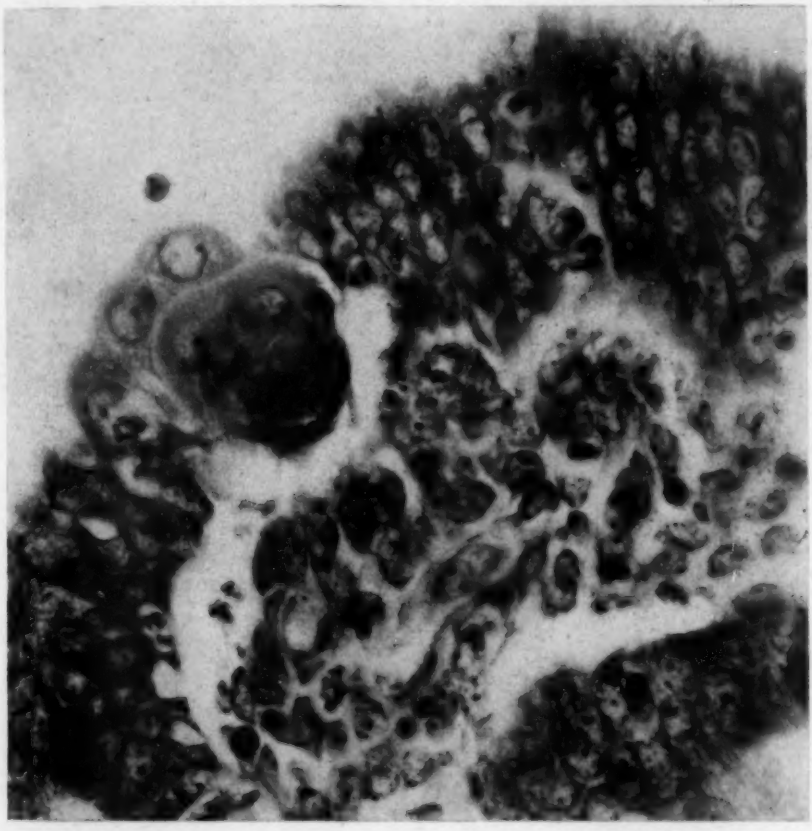

Fig. 10 (guinea-pig 2).—Section of the uterus showing the early focus of epithelial substitution; × 850. The animal was fed on the experimental diet for 66 days. At the beginning of the experiment it was 146 days of age and weighed 590 Gm. The maximum weight was 650 Gm.; the final weight, 300 Gm.

thyroid and suprarenal glands were normal. The thyroid and the pancreas showed slight atrophy as compared with those glands in the rat. The spleen did not show any marked change in size. Microscopically there was a heavy hemosiderin accumulation within the phagocytic cells. The bone marrow was active, but without evident departure from normal. An outstanding difference is that none of the guinea-

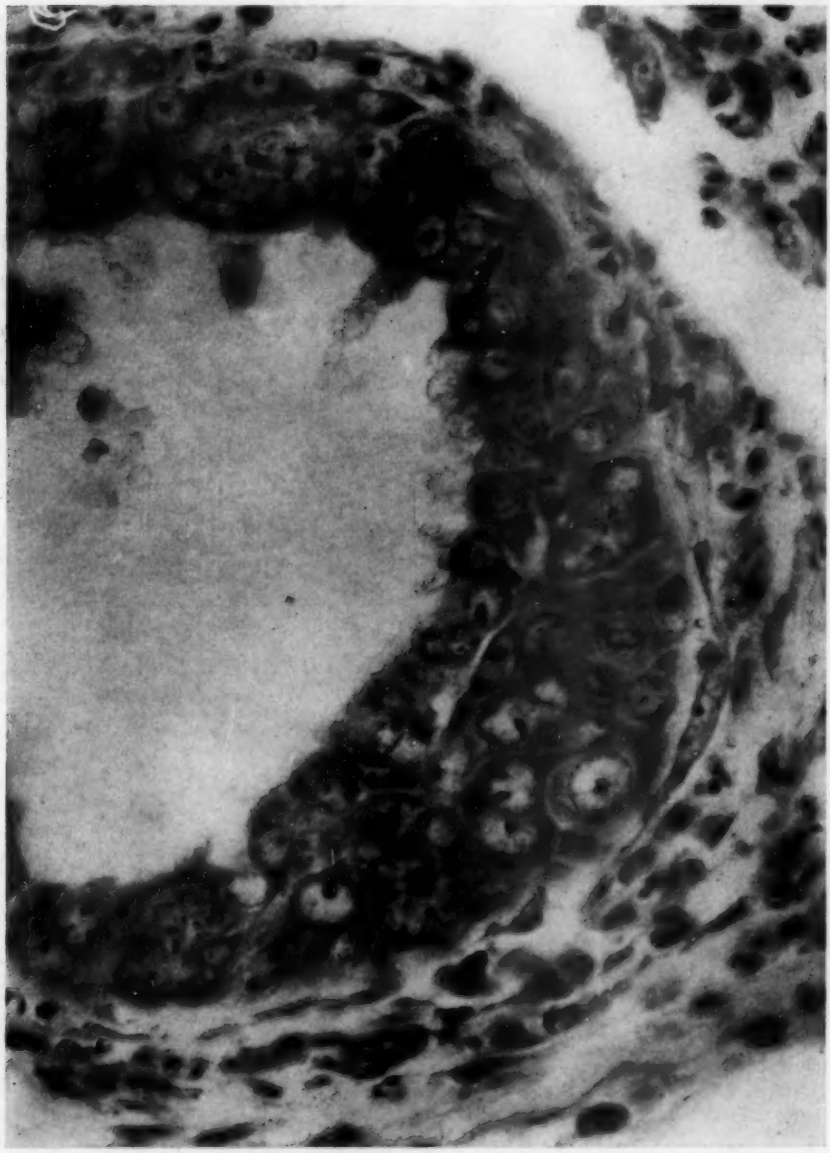

Fig. 11 (guinea-pig 2).—Section of the submaxillary gland duct showing early focus of epithelial substitution; × 850.

pigs showed formation of keratinizing epithelium in the parocular glands or their ducts. The meibomian glands and the corneas remained normal in every instance. Mucus-secreting cells, often atrophic in appearance, of the palpebral conjunctivae persisted in every instance.

As in the rat, keratinizing epithelium was found in the respiratory tract, in the nares, larynx, trachea (figs. 6 and 7) and bronchi; in the alimentary tract, in the submaxillary glands (figs. 4 and 5), the parotid glands and the accessary salivary glands of the tongue and pharynx; in the genito-urinary tract, in the bladder (fig. 8), ureters, pelves of the kidneys, uterus (figs. 2 and 3), oviducts, epididymis, prostate, seminal vesicles and coagulating glands. Of the ductless glands, the thymus alone showed changes; there were marked atrophy and greatly enlarged Hassall's corpuscles (fig. 9).

In contrast to the rat, extensive formation of keratinizing epithelium was found before pronounced atrophy of the organs concerned had occurred and in the presence of considerable amounts of normal appearing fat distributed throughout the body. The early and extraordinary degree of change in the bladder and in the uterus of the guinea-pig was another obvious difference as compared with rats. Atrophy of graafian follicles and ova was constant, in contrast to our observations in the rat.

The histologic sequences were the same as in the rat and were carefully studied, particularly in trachea, salivary glands and uterus.

The formation of the keratinizing epithelium begins simultaneously or in sequence in many foci. The first change is demonstrable in the presence of groups composed of several cells deep in the epithelium, probably the result of division of intercalated cells (figs. 10 and 11). The cells of these groups are characterized by deeply basic straining cytoplasm and nuclei larger than normal for the particular epithelium. They increase by mitotic division and differentiate forming foci of stratified keratinizing epithelium—sometimes resulting in "pearl" formation usually extending and undermining the pre-existing epithelium. Growth rate is apparently augmented as indicated by numerous mitotic figures, the rapid accumulation of desquamated keratinizing cells and the downgrowth into supporting tissues. The observations made on the tissues of the guinea-pig suggest even more forcibly than those in rats that the growth of the replacing stratified epithelium is rapid and continuous and not responsive to the balancing or regulatory factors which control normal covering epitheliums. The proliferation of epithelium in vitamin A deficiency will be considered in a separate paper.

CALCIFICATION OF THE LIVER

WITH REMARKS ON THE CAUSE OF CALCIFICATION IN GENERAL *

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Some years ago I discussed calcification of the lungs as a distinct disease,[1] caused, it was thought, by a primary constitutional or metabolic disorder. I have been quoted incorrectly by H. G. Wells [2] in that I am made to explain the calcareous deposits in this case as due to chronic renal disease. This erroneous statement is repeated by Hueper.[3] Recently, my interest in calcification was stimulated again when I observed a most extensive calcification in the liver in a patient with malignant granulomatosis. The history of the case in question follows:

REPORT OF CASE

History.—A boy, whose mother died of tuberculosis, became ill in 1923, with swelling of the lymph nodes of the neck and later of the axillae. In 1924, he entered a hospital for patients with tuberculosis (Dr. Sundt). When admitted he had a papulous eruption of the skin; the lymph nodes were rather small, not tender and not bound to the surrounding tissues. The liver and spleen were not enlarged. There was some fever. He was subjected to treatment by rays and by light and sun; arsphenamine was also administered. At first, there was some improvement with an increase in weight. The Wassermann and the Pirquet reactions were negative. There was a slight anemia, but the blood picture in general was normal. Microscopic examination of the lymph nodes showed the picture of malignant granulomatosis with eosinophils and small multinuclear giant cells. The inoculation of bits of lymph node into three guinea-pigs was without effect. The boy became worse, anemic and emaciated, and the spleen and liver enlarged, until his death in November, 1926.

Examination.—The lymph nodes of the neck and chest, along the trachea, at the hilum, and along the bronchi were hard, almost fibrous, and enlarged up to the size of a walnut. In some of them were yellowish white necrotic areas. In the posterior edge of the upper lobe of the right lung and toward the hilum of the left lung were hard and dry yellowish white infiltrations. In the anterior mediastinum was a hard mass, as large as a fist, which surrounded the thymus and infiltrated the trachea, the anterior wall of the esophagus and the posterior

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* From the Pathologico-Anatomical Institute of the University of Oslo.

1. Harbitz, Francis: Extensive Calcification of the Lungs as a Distinct Disease, Norsk. Mag. f. Lægevidensk. **78**:1129, 1917; Calcification of Lungs, Arch. Int. Med. **21**:129 (Jan.) 1918.

2. Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920, p. 443.

3. Hueper, W. M.: Metastatic Calcification in the Dog After Injection of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

surface of the sternum. This mass contained whitish or reddish-brown nodules, and near the upper edge was a mass the size of a hazelnut, with a calcified capsule surrounding semigelatinous material. The retroperitoneal lymph nodes were enlarged, hard and gray and grayish white with yellow infiltration. The spleen weighed 450 Gm., its form being abnormal, with a large mass at one end; it contained confluent grayish and whitish nodes. The liver was much enlarged, was deformed and weighed 3,100 Gm. The surface was smooth, and the usual liver color showed yellowish-white patches, these patches being grains of calcification separated by brownish-red liver substance. The greater part of the liver, but especially the posterior parts, was stony hard. These hard areas merged into

Fig. 1.—Roentgenogram of liver showing calcareous deposits.

the softer tissue without sharp limits. The surface of the hard parts was rough and gritty. The biliary ducts seemed to be normal. The kidneys weighed 180 Gm., were smooth and grayish white, the markings being somewhat indistinct. The suprarenal glands, the thyroid, and the pancreas seemed to be normal, but the suprarenal glands were unusually firm. The bones were not softened, but they were not examined microscopically.

Microscopic examination of the lymph glands and the spleen showed a typical picture of malignant granulomatosis, with scar tissue, giant cells of various form and size, eosinophils, lymphocytes, leukocytes and plasma cells. Nowhere was there any sign of tuberculosis. In some of the lymph nodes from the neck calcified masses were found. In the necrotic areas in the spleen was a large amount of yellowish-brown amorphous pigment but no calcareous deposits. The

yellowish-white areas in the lungs contained calcareous ring-shaped masses and clumps. The kidneys showed infiltrations with lymphocytes and leukocytes extending from the cortex downward into the medulla, with swelling and degeneration of the stroma and the walls of blood vessels, and in places calcareous deposits. The remnants of the thymus did not show anything abnormal, and the parathyroids seemed normal. The suprarenal glands, on the other hand, showed a considerable calcareous deposit, in the form of clumps and masses. In Kossa's preparations for calcium phosphate, there was an extensive precipitation of black clumps and fine grains.

The liver contained the most marked changes. Outside the calcified parts, the structure was, on the whole, normal. Near the calcified areas there was some

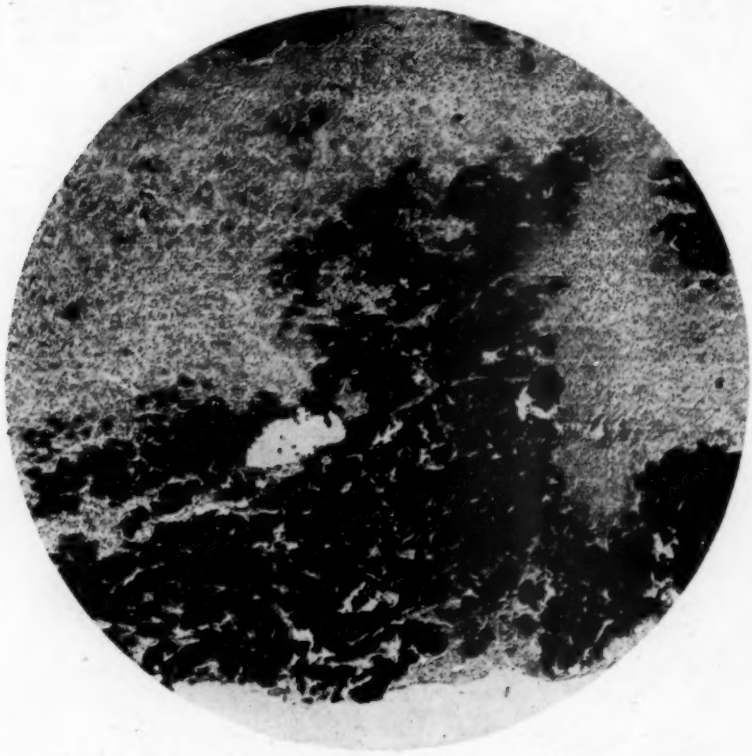

Fig. 2.—Calcareous deposits in the suprarenal glands; × 60.

degeneration of the liver cells, and between the cells, and apparently also in the capillaries, was a hyaline substance that stained violet with hematoxylin. Between the clumps of calcareous matter were small islands of atrophic or degenerated liver tissue without any signs of inflammation. In the liver, also, Kossa's preparation for calcium phosphate gave precipitation of black grains and clumps.

As has been shown, there were calcareous deposits of phosphate and doubtless also of carbonate of lime in the liver, lungs, suprarenal glands, lymph nodes, kidneys and capsules of the thymus. In the liver there was a homogeneous hyaline substance, special staining of which with methyl violet gave an intense red, indicating that amyloid substance was present. Scanty deposits of similar material were found in the walls of the vessels in the spleen, in some places in the follicles and in the suprarenal glands, but not elsewhere.

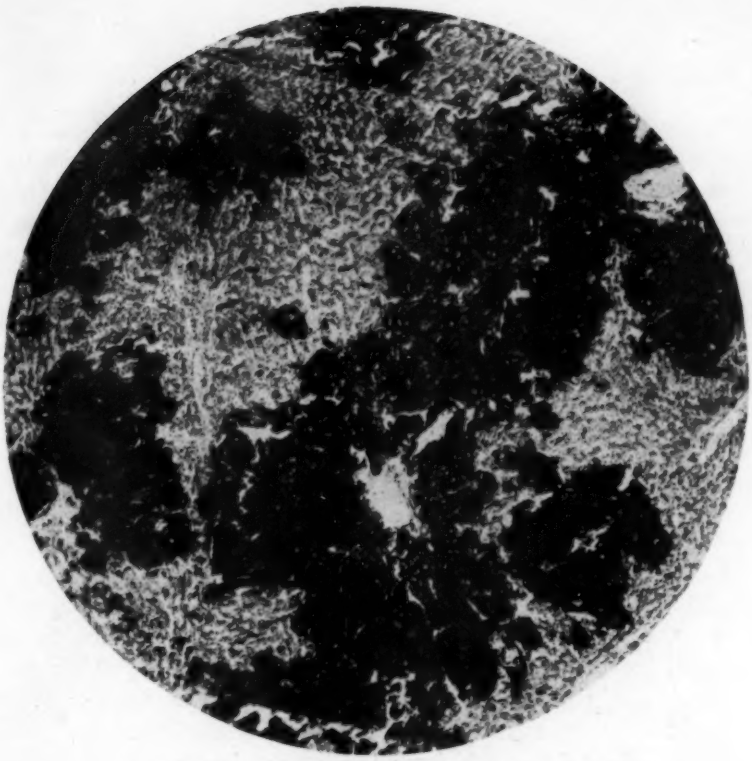

Fig. 3.—Calcareous deposits in the liver; × 60.

Fig. 4.—Reaction in the liver to Kossa's preparation, showing small black calcareous granules in hyaline substance (amyloid) surrounding liver cells; × 60.

Parts of the calcific areas in the liver were examined by Mr. Skaar in Professor Torup's Physiological Institute, and the composition of the calcareous material was found to be 65.41 per cent solid matter, which consisted of 23.72 per cent organic and 70.28 per cent inorganic matter; the latter contained 35.59 per cent calcium and 7.03 per cent phosphate. If it is assumed that phosphate is present as orthophosphoric acid and probably bound to calcium as tricalcium phosphate, then 100 Gm. of ash would contain 35.15 Gm. of tricalcium phosphate, which represents 13.829 Gm. of calcium, leaving 21.761 Gm. of calcium per hundred grams of ash. Assuming, further, that this last calcium is found as calcium carbonate, there would be 54.4 Gm. of calcium carbonate in 100 Gm. of ash. Of 100 Gm. of ash 89.55 Gm. would consist of phosphate and carbonate, the remaining 10.45 Gm. consisting of magnesium, sodium and potassium. Accordingly, 100 Gm. of solids consisted of 29.72 Gm. of organic substance, 24.70 Gm. of tricalcium phosphate, 38.23 Gm. of calcium carbonate and 7.25 Gm. of magnesium-potassium-sodium compounds. Professor Torup remarks that the great amount of inorganic substances is of interest, first, because bones, for example, contain from 48 to 70 per cent of inorganic substances; second, because the ratio between the phosphate and the carbonate is as 100 to 150, while in ash from the human femur the relation is as 100 to 12; hence, the calcareous deposit of lime in the liver is mainly in the form of calcium carbonate.

The analysis of the calcified lungs, which I described,[1] gave 78.05 per cent of ash, which consisted of 18.3 per cent of calcium carbonate, and about 80 per cent of calcium phosphate. In certain forms of gout, the large amounts of lime that may be found in the subcutaneous tissue consist mainly of calcium phosphate with a smaller amount of calcium carbonate.

What is the explanation of the extraordinary calcification in the liver in the case reported? The following factors may be considered:

1. Increased destruction of bone resulted in the transfer of calcium salts by the blood. Such destruction of bone cannot be considered here, and it should be noted that the blood normally is saturated with calcium.

2. Chronic nephritis might be of significance, but not because calcium salts are stored in the blood, because most of the salts are excreted through the intestines, especially the large intestine. Nephritis, however, may be of importance in causing changes in the blood, both chemical and physical. It would not seem reasonable to ascribe any importance to changes in the kidney in the case reported.

3. Diminished content in acid and increase in alkali may be of significance, especially in organs that excrete acids, such as the lungs (carbon dioxide), the stomach, especially the fundus (hydrochloric

acid), and the kidneys (phosphate salts). The liver, however, does not excrete acids to any extent. This organ is also rarely the seat of calcareous deposits. Schober,[4] in 34 cases, found deposits in the liver in 2, in the lungs in 28, in the kidneys in 17, in the stomach in 9 and in the heart and larger arteries in 6.

4. Calcium salts may be deposited because certain tissues may have a special affinity for them, as, for example, cartilage, connected tissue, elastic tissue and basal membranes.

Fig. 5.—Amyloid material in the liver around calcareous masses; × 280.

5. Of special interest are disturbances in internal secretion which may cause an abnormal metabolism of calcium. It is known that the parathyroid glands regulate the metabolism of calcium, and that removal of them leads to increased excretion of calcium and an increase of calcium in the blood, with disturbances of ossification; and it may be supposed that a hyperplasia might cause an increase in calcium, just as injection of extract of parathyroid in animals causes calcification, especially in the stomach, kidneys, lungs, heart muscle and thyroid. In the

4. Schober: Ueber Kalkmetastasen, Dissertation, Breslau, 1914.

case reported changes had not occurred in the one parathyroid that was examined, and the thyroid gland and the thymic remnants were normal, but there was a deposit of calcareous matter in the suprarenal glands, with some degeneration of the suprarenal tissue; but whether this condition was of any significance remains doubtful.

6. The question arises whether a constitutional anomaly or metabolic disease such as is supposed to accompany gout was present. There might be a peculiar physicochemical state of the blood plasma, either congenital or acquired.

7. In the case reported, a serious and fatal disease existed in the form of a malignant lymphogranulomatosis, and it is possible that this disease gave rise to metabolic disturbances at the same time that it caused degenerative and necrotic changes in the tissues in which calcium is prone to be deposited. Products like hyalin and fibrin seem to attract calcium, and peculiar calcium complexes may be formed, as for example, in arterial walls and in degenerated connective tissue.

In the case under consideration an amyloid degeneration appears to precede calcification in the liver. This is rather remarkable because, according to experience, amyloid degeneration does not favor calcification. It is true also that in malignant lymphogranulomatosis amyloid degeneration is rather rare. Possibly special influences which have not been recognized were present in this case. Disintegration of cells may have led to changes in the plasma of the blood owing to the absorption of cellular products. It is recalled that the patient was subjected to treatment with rays and with light; particularly the treatment with rays may have caused destruction of cells. It is also suggested that the amyloid substance in this instance may have had peculiarities of composition that attracted calcium salts. Unfortunately, a chemical study of the blood was not made during life. It would be well in similar cases and in cases of calcification in general to make a careful chemical examination of the blood during life.

SUMMARY

A case of malignant lymphogranulomatosis in a boy, aged 16, with extensive calcification in the liver, is described. The cause of the calcification remains obscure, and the need of chemical examination of the blood during life in cases of abnormal calcification is emphasized.

CYSTADENOMA OF THE PANCREAS*

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Pancreatic cysts are not rare. Recently Müller [1] was able to collect about 460 cases from the literature. These cysts, most of which are pseudocysts, fall into the following groups:

1. Cystadenomas
2. Dysontogenetic cysts
3. Retention cysts
4. Pseudocysts
5. Traumatic blood cysts
6. Echinococcus cysts

Cystadenomas of the pancreas are true tumors. They are rare (twenty-four have been recorded, according to Müller) and occur as single or multiple growths. Usually, they are surrounded by a thick, fibrous capsule. The lumen in the cystadenomas is filled more or less with papillary proliferations, lined by a cubical or cylindric epithelium, which originates from the epithelium of the ducts. Islands of pancreatic tissue and pancreatic ducts are frequently present in the fibrous capsule.

Dysontogenetic cysts result from disturbance of the embryonal development; they represent malformations, and are usually associated with similar alterations in the liver and the kidney. A cystic degeneration of aberrant ducts must be considered the cause of this condition, which involves the whole pancreas.

Retention cysts are distended ducts in the genesis of which not only the retention of the pancreatic secretion, but also an active proliferation of the lining epithelium, may be of importance according to Wegelin.[2] They are single or multiple and are the result of obstruction of the ducts. A blockade of the duct of Wirsung sometimes results in the formation of cysts along the course of this duct in the form of a rosary (ranula pancreatica). The obstruction may be due to various causes. The most frequent and most important one is chronic interstitial pancreatitis, which may follow a syphilitic infection, arteriosclerosis or other toxic vascular diseases, or which is produced by the extension of an

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1. Müller: Zur Lehre von den Pankreascysten, Arch. f. klin. Chir. **143**:285, 1926.

2. Wegelin: Zur Gemese und Entstehung der Pankreascysten, Verhandl. d. deutsch path. Gesellsch. **18**:169, 1921.

inflammatory process in the adjacent organs into the substance of the pancreas (cholecystitis, gastritis). The pressure of the increased interstitial tissue and the swelling of the mucosa of the ducts produce occlusion of the lumen with retention of the secretion. Concretions may block the lumen of the ducts. Furthermore, the pressure and the invasion of tumors, especially carcinomas of the head of the pancreas, may block the ducts. Finally, pressure from outside the pancreas, as by adhesions, gallstones and tumors of adjacent organs, may produce an obstruction of the pancreatic ducts and consequently retention cysts. These cysts have a thin, fibrous wall lined by a cubical or cylindric epithelium, which may be lacking, partly or completely owing to pressure atrophy and digestion when the cysts reach larger dimensions. Distended pancreatic ducts are often seen in the chronically inflamed pancreatic tissue surrounding the cysts.

Pseudocytes are the results of degenerative or purulent processes in the pancreas. Chronic interstitial pancreatitis must be mentioned also as one of the causative factors. The narrowing of the lumen of the blood vessels in the course of this disease may produce circulatory disturbances and thrombosis, which are followed by degenerative changes and necrosis of the parenchyma. The secondary autolysis of the dead tissue results in the formation of a cyst which is surrounded by a fibrous wall originating from proliferated interstitial connective tissue. Moreover, an acute necrosis of the pancreas may give the same end-result, which is due to sequestration of pancreatic tissue and liquefaction by the pancreatic ferments. Finally, encapsulated inflammatory exudates in the pancreas may form pseudocysts. Primary blood cysts of the pancreas have a traumatic origin. Cysts with a bloody content originating from an eroded vessel in the course of degenerative and autodigestive and inflammatory processes do not belong to this group. Blood cysts are more frequent in men than in women. Usually they are noticed from three to five weeks after the trauma, and are most frequent in persons between 10 and 30 years of age, because, as Honigmann [3] states, the pancreas is more vulnerable in young persons than in old ones.

Echinococcus cysts are rare and represent only 6.5 per cent of all pancreatic cysts and 0.12 per cent of all echinococcus cysts (Müller [1]). There are forty-two cases on record.

The content of a pancreatic cyst varies greatly in character, appearance and composition, regardless of the type. The reaction is alkaline. The specific gravity is usually between 1,010 and 1,015, but may go as high as 1,030. The fluid may be colorless, but is more often yellowish or brownish; admixture of blood, which is rather frequent, produces a

3. Honigmann: Zur Kenntnis der traumatischen Pankreascysten, deutsch Ztschr. f. Chir. **80**:1, 1905.

sanguinolent appearance. The character may be serous, mucoid, jelly-like, foamy or beerlike. Sometimes soapy masses and necrotic pancreatic tissue are found in the fluid. The microscopic examination does not show any characteristic objects (blood corpuscles, detritus, pigmented scales, cholesterol crystals, hemoglobin crystals, etc.). Chemical examination reveals albumin, sometimes as high as 10 per cent. Mucus, fat, uric acid, urea and urobilin may also be found. Tests for pancreatic ferments may or may not be positive. Trypsin is usually absent; but the test for trypsin is rather unreliable, because blood serum in the content inhibits the tryptic action. Moreover, the trypsin is not present as trypsin, but as trypsinogen which has to be activated by the addition of the intestinal ferment enterokinase to reveal the presence of trypsin in the proper tests. Steapsin and diastase are more frequently found. The positive or negative result of these tests for pancreatic ferments does not decide whether the cyst is a true one or whether it is merely a pseudocyst. The amount of fluid content varies from a few cubic centimeters, in cysts as large as a hen's egg, to 22 liters in cysts filling the abdominal cavity.

Pancreatic cysts are usually observed in the left upper quadrant of the abdomen. They may originate in the head, the body or the tail of the pancreas or may involve several or all parts of it. While Müller [1] reports that they are more frequent in the head of the pancreas, Umber [4] states that they are more often seen in the tail. They may extend into the ligamentum gastrohepaticum, between the membranes of the mesocolon, into the retroperitoneal space between the stomach and the transverse colon, the most frequent way, and into the bursa omentalis.

The clinical symptoms may be summarized as follows: Loss of appetite, loss of weight, dyspnea, pressure and pains in the gastric region, belching, vomiting, obstipation, which may reach an ileus-like character, radiating pains in the abdomen from pressure on the celiac ganglion, jaundice, ascites from pressure on the portal vein, oliguria or anuria due to compression of the ureters, bronzing of the skin, diarrhea and increased temperature. The blood may show increase of the blood sugar and the diastatic ferment. Eosinophilia and a positive complement-fixation test for echinococcus are significant. An increased amount of fat, starch and muscle fibers in the stool are evidence that the cyst interferes with the external secretion of the pancreas. The urine may show glucose in cases in which the internal secretion of the pancreas is impaired. The two latter complications are rare. Palpation of the abdomen reveals a round tumor with a smooth surface, elastic consistence and little or no movability. The latter symptom seems to be quite

4. Umber: Handbuch der Inneren Medizin, Mohr and Staehelin, 1926, ed. 2, vol. 3, part 2, p. 237.

characteristic and constant, because, according to Müller, only seven cases are reported in which the cysts were freely movable. In a few cases, respiratory movements have been observed. Fluctuation in the tumor can usually be demonstrated. In general, the cyst does not extend beyond the umbilical region and is not well definable from the adjacent organs. Inflation of the stomach and of the colon, as well as the establishment of a pneumoperitoneum, may facilitate the correct diagnosis. The demonstration of the independence of the movements of the cyst from the location of an ureteral catheter inserted into the pelvis of the kidney may help to exclude renal tumors. Such observation is of special importance because pancreatic cysts sometimes compress the ureter and cause hydronephrosis, a complication which may greatly interfere with the correct diagnosis of the primary condition.

Carcinomatous development in the wall of pancreatic cysts has been observed seven times.

When differential diagnosis is made, a large number of cystic formations in the abdominal cavity must be considered: cysts of the spleen, of the mesentery and omentum, echinococcus of the liver and of the bursa omentalis, cystically degenerated lymph nodes of the abdomen, retroperitoneal teratomas, cystically degenerated solid tumors, such as carcinomatous metastases of the abdominal cavity, aneurysm of the abdominal aorta, cholecystitis, ovarian cysts, hydronephroses, enterocystomas, etc.

Four methods of treatment are employed:

1. Sewing of the cyst to the abdominal wall, incision and drainage of the cyst. This procedure always leads to a disagreeable complication, a fistula of the pancreas which produces an eczema of the skin and is usually of a long duration.
2. Total extirpation of the cyst.
3. Partial resection of the cyst.
4. Anastomosis between the pancreatic cyst and a loop of small intestine.

REPORT OF CASE

Mrs. C. W., aged 33, a patient of Dr. Sawyer, was admitted to Mercy Hospital in April, 1923. The menses had always been irregular and painful for from six to seven days. For many years, she had had pains in the back. Six years before admission to the hospital, appendectomy had been performed. During the last fourteen days, there had been severe pain in the abdomen, which had radiated into the left leg and hip. Constipation had also been present during the last ten days. A few weeks before, she had noticed a fist-sized tumor in the left epigastric region just below the arch of the ribs. Her appetite was good and she did not have headache or any urinary trouble.

There was a round, movable tumor of elastic consistence and with a smooth surface in the left epigastric region. The tumor could be moved downward below the umbilical region, but its exact location could not be determined. The roentgenogram showed a marked indentation of the transverse colon near the splenic flexure, due to a mass on its anterior side. The kidney was free from calculi. The renal function test resulted in the excretion of 72 per cent of the injected

phenolsulphonphthalein. The urine was free from albumin and casts, but leukocytes were present in a large number. The blood was normal. The preoperative diagnosis was "tumor of the left kidney." At operation, the kidney was found to be horse-shoe shaped and greatly enlarged. The superior pole was swollen, and a cystic condition was found on opening the kidney. Microscopic examination showed a normal renal structure. After an uneventful recovery, the patient left the hospital, but returned in January, 1927, with the following complaint: During the last three years, there had frequently been gastric distress, occasionally nausea, but no vomiting, and pain in the lumbar and left renal region. A tumor mass was found in the left renal region. This mass was movable but not painful on pressure, and disappeared completely when the patient was lying down and the tumor was pushed upward. Roentgen-ray examination showed the left kidney in a normal position and of normal shape. There was a shadow about the size of a coconut in the left lower quadrant, apparently below the lower pole of the left kidney. In the pyelogram, the ureteral

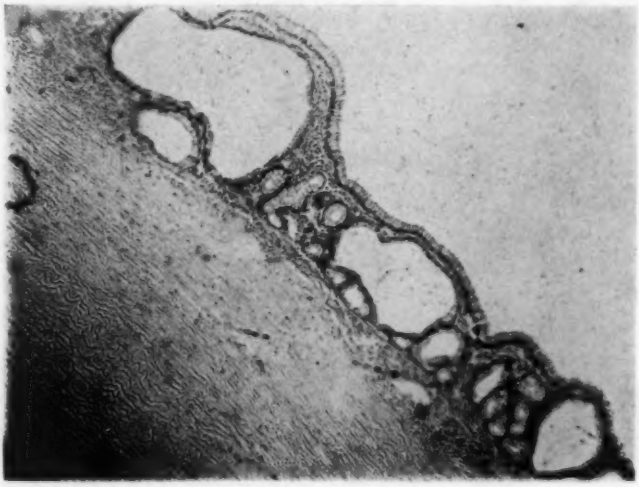

Fig. 1.—Wall of the cyst.

catheters were in normal position. The pelvis was normal in size and shape. There was considerable deviation of the left ureter toward the midline, which possibly was due to pressure. Culture of the urine from the left kidney showed staphylococci. The urine contained albumin, leukocytes and few erythrocytes. The capsule of the left kidney was firmly adherent. A tumor the size of a grapefruit was found floating almost free between the diaphragm and the pelvis. The pedicle of the tumor was formed by the elongated tail of the pancreas to which the cyst was attached. The growth proved to be a cystic tumor the size of a large fist, round, elastic in consistence and yellowish-gray. The outer surface was smooth, with the exception of that part by which the tumor was attached to the pancreas and to the retroperitoneal tissue. Some fat tissue and some pancreatic tissue were adherent to the capsule. A dense network of hyperemic vessels ran underneath the serosa. The wall was about half a millimeter thick on cross-section, and was composed of a strong, fibrous tissue which was thin and somewhat translucent in places. The content was a serous, colorless fluid. The inside of the cyst showed many small and large pouches,

the largest one about the size of a hazelnut. Trabeculae which frequently crossed each other were present in a large number. In some parts, numerous small translucent papillary and vesicular nodules reaching the size of a rice seed covered the inner surface.

Microscopic Examination.—The inside of the cyst was lined by a cylindric epithelium. The nuclei of the cells were located at the base and had the shape of a short rod. In cells which contained a large vacuole, they were pressed against the wall and flattened. In places which corresponded with the macroscopically visible nodules, small glandular and cystic formations were found underneath the cylindric lining (fig. 1). In other places, the cylindric lining was lacking and a loose connective tissue with scanty round cell infiltrations and hemorrhages formed the inside of the cyst. The middle layer of the capsule was made up by a strong, hyalinized connective tissue in which small cystic glands were occasionally observed. The peripheral layer of the wall was composed of a loose connective

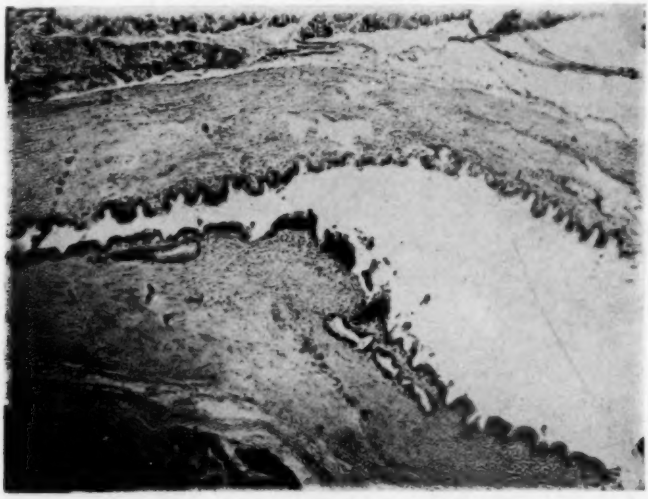

Fig. 2.—Cystic, distended duct with papillary proliferation of the epithelium.

tissue containing many vessels and occasionally small lymphocytic infiltrations, as well as small scattered nests of normal pancreatic tissue. The pancreatic tissue adherent to the capsule was normal, except that there was an increase of the interstitial connective tissue and a lymphocytic infiltration of minor degree. The ducts were somewhat distended and sometimes formed small cysts, the epithelial lining of which frequently showed solid papillary formations. Proliferations of ducts around these cysts were noteworthy (fig. 2).

The diagnosis was cystadenoma of the pancreas and chronic pancreatitis.

SUMMARY

The cystadenoma in this case is regarded as primary and the inflammatory changes in the adjacent pancreatic tissue as secondary due to the pressure of the tumor on the ducts, with obstruction and cystic distention. A correct preoperative diagnosis was not made, because the tumor had caused a hydronephrosis by pressure on the ureter.

POLYMORPHONUCLEAR NEUTROPHILS IN THE BLOOD IN LYMPHADENOPATHIES

THEIR RELATION TO CLASSIFICATION AND RADIATION TREATMENT *

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The observations presented in this article are intended to show that in diseases of the lymphatic glands the neutrophils may exhibit percentages and actual figures that are of value in diagnosis, and that the behavior of these cells under radiation treatment may be useful in the control of exposure to the roentgen ray. In addition, the data may assist in the classification of the entire obscure group of the leukemias, lymphatic tumors and lymphogranuloma.

The number of cases presenting morbid lesions in the lymphatic structures is increasing, judging by the number seen in large clinics and radiologic institutes, or, if the incidence is not greater, the number seems to grow because the knowledge of cause, classification, diagnosis and treatment remains the same. The lack of increased understanding is due largely to the indefiniteness of some of the varieties, somewhat to the chronicity of the diseases, but in no small part to the fact that there is a method of treatment that gives symptomatic relief for long periods. Ever since Senn demonstrated the value of the roentgen ray in the treatment of leukemia, it has been the fashion to pass the patient on to the radiologist, who proceeds to make life more comfortable for the patient, and incidentally to relieve the conscience of the clinician. But the radiologist is honest enough to admit that beyond gaining a knowledge of how radiant energy affects gross morbid lesions and reduces circulating leukocytes, he has added nothing to the knowledge of the essence of these diseases. The work of Minot [1] indicates clearly that all that can be expected from radiation treatment is comfort, reduction of complication and possibly a slightly increased expectation of life.

Because of the known low resistance in lymphatic leukemia to infectious disease, of which I have had two striking examples, and because I feel that the inevitable end of one case of lymphadenosis was hastened,

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1. Minot, G. R., and Isaacs, R.: Lymphoblastoma (Malignant Lymphoma); Age and Sex Incidence, Duration of Disease, and Effect of Roentgen-Ray and Radium Irradiation and Surgery, J. A. M. A. **86**:1185 (April 17) 1926; Boston M. & S. J. **191**:1, 1924.

my attention was drawn to the neutrophils of the blood as possible indicators of the resistance or lack thereof in these cases. The results have been instructive so far as individual cases were concerned and they may be of significance in classification and in controlling radiation treatment.

The polymorphonuclear neutrophil reaction is the best indication of response to infection and of the activity of the bone marrow in this direction. The numeric variations of neutrophils do not run parallel with those of hemoglobin or red blood cells, for in certain infectious states the first may rise, the others fall. Contrariwise, as shall be seen, in certain leukemias, neutrophils may fall and the red cells and their coloring matter may remain high. This would indicate that the apparatus involved in the production of neutrophils and of erythrocytes are independent. So, too, the production and destruction of neutrophils and of lymphocytes are, in the adult at least, unrelated. Nevertheless, the behavior of polymorphonuclear cells is different in different forms of lymphadenopathy, and their behavior with radiation treatment is not the same in all varieties.

Before proceeding with the details of cases forming the basis of this report, it will be well to discuss briefly, first, the classification used and the methods employed to reach diagnosis, and, second, the accepted known effects of radiation on the cells and tissues involved in these diseases.

One may find almost as many classifications as there are serious students of lymphadenopathies, which condition is due to the bewildering variety of clinical and pathologic manifestations. There seems to be a gradation, in the sense of morbid anatomy at least, from the chronic lymphatic hyperplasias of simple benign character, possibly in response to an infectious virus, to the unrestrained malignant proliferation illustrated by lymphosarcoma. This view would imply the probability of identity in the causative agency of many, if not all, chronic lymphatic hyperplasias. Such may be the case, but one is far from such a decision. Nägeli accepts this view with reservations because of apparent transitions of one well defined state of certain cases into another equally definite pathologic and clinical type, for example, a local lymphosarcoma becoming leukemic or a simple lymphadenoma resulting in sarcoma. The present proposal for classification by the Lymph Gland Registry admits benign, borderline and malignant lymphatic hyperplasias, but they are as yet based entirely on microscopic appearances. Sternberg differs from this view, believes that there are clinical and pathologic characters that one should be able to identify, and objects to the idea of transition stages, although he admits the existence of borderline cases. Ewing's position seems to be that one should attempt to specify types in order to learn more about each one. In our clinic

the classification of the serious varieties that demand radiation treatment has been as simple as possible; at the same time an attempt has been made to distinguish the main types, admitting that many cases partake of the characters of related forms. Only the criteria relied on in judging the diagnosis of the cases used in this article will be given, since the reaction of the neutrophils is the principal subject of the study.

Chronic lymphatic leukemia is characterized by disproportionate lymphocytosis, moderate lymphadenopathy, moderate or absent splenomegaly, chronicity and favorable action to radiation.

Sublymphemic leukemia is similar, but the number of circulating leukocytes is only moderately increased with, however, absolute and relative lymphocytosis. Enlarged lymph nodes are more prominent in this condition.

Aleukemic lymphadenosis is generalized lymphadenopathy without leukocytosis, lymphocytosis and splenomegaly, or only slight enlargement of the spleen. The lesions are not so uniformly distributed as in leukemia proper, they often being irregularly scattered and with definitely less tendency to involve the liver, kidney and spleen. Some writers (Nägeli and others) think that this condition may be one phase of leukemia, but others (Ewing and Sternberg) credit it with being a fairly well defined entity. My results would favor the latter idea. Indeed, the condition approaches lymphosarcoma rather than leukemia. Certain cases end in marrow lesions and bone tumors akin to myeloma. All cases of chronic lymphadenopathy, especially when the patients suffer vague pains, should be studied for osseous lesions. Little has been recorded of bony changes in lymphatic leukemia.

Leukosarcoma is a local lymphatic tumor, with leukemia, of rapid course and with a tendency in the late stages to involve the same tissues —spleen, liver, kidneys and marrow—as are affected in leukemia. Its micro-anatomy is identical with leukemia, and I have called it "local leukemia." Its reaction under the roentgen ray is poor.

Lymphosarcoma is a local tumor of varying rate of growth tending to involve all adjacent tissue (heteroplastic, Sternberg maintains), without leukemia. Nägeli states that the lymphocytes are low. It is disseminated to places not especially favored by leukemia. The reaction under roentgen-ray treatment is good. Microscopically, the lymphoid cells of lymphosarcoma are separated and supported by a fine fibrous tissue stroma that seems to grow with the tumor. In leukemia and in the one leukosarcoma that I have studied, interstitial framework does not exist beyond that normal to the tissue invaded.

Hodgkin's disease is a widespread growth in lymphatic tissues usually with local manifestations at the beginning but shortly becoming general, attended by polynucleosis, an approximately normal number of lymphocytes, early anemia and chronic course. The cellular stage or

variety reacts well with radiation treatment, the fibrotic type, poorly. Certain cases assume a rapid phase with the appearance of a histology like round or spindle cell sarcoma.

Endothelioma may affect gland groups or be generalized in the lymphatic glands. The clinical picture is varied. So far as is known there is no typical blood picture.

All varieties of sarcoma may occur in the lymph nodes, springing from reticulum or supporting tissue. There is no typical blood picture; polynucleosis is frequent.

The diagnosis in the cases reported here was made by clinical history supplemented by bioscopic adenectomy in every case. A few cases were subjected to autopsy, with partial or complete confirmation, a few are untraced and the remainder of the patients are living.

Bone marrow involvement in lymphatic hyperplasias is not a pathologic feature of great frequency, as judged by early and pronounced anemia, although the platelets may be decreased and coagulation retarded. Despite this, neutrophils, products of the bone marrow, are low in number in lymphatic leukemia, a condition that suggests an action of the virus or agency that depresses the activity of the marrow. In late stages of leukemia, deposits and infiltrates of lymphoid cells are combined with marrow atrophy or aplasia, mixed with abortive attempts at hyperplasia to make enough blood cells. In the so-called pseudoleukemic states, the marrow and bone itself may be involved by tumor-like nodules of lymphoid cells or, in the case of Hodgkin's disease, of characteristic histology. This feature will assist in the distinction of leukemia and its immediate relatives—leukosarcoma and sublymphemic or aleukemic leukemia—from lymphadenosis and sarcoma. This will be emphasized later. Involvement of the marrow by secondary neoplasms usually results in a circulating polynucleosis.

The involvement of the marrow and its myeloid series of cells and the behavior of these elements under radiation, in relation to lymphadenopathies, deserves for its understanding a brief review of what radiant energy does to the neutrophils and to the important cellular unit of the diseases in question, the lymphocytes. So far as the kind of cells produced under normal and leukemic conditions is concerned, the cells evidently do not differ in a biologic sense. Their capability of function as phagocytes and enzyme carriers is essentially the same. Hektoen seems to think that the neutrophils of lymphatic leukemia are perhaps above normal in phagocytic power, while in myelemia they are rather lower. The scant evidence in the literature that there is any phagocytic variation in normal and radiated neutrophils is contradictory. The inflammatory exudates after radiation consist of the same types of cells as when radiation has not occurred.

The effect of radiation on lymphoid cells was first completely described by Heineke.[2] He showed the destruction of small mononuclears in circulation and in lymph follicles, the fragmentation of lymphoblasts and the phagocytosis of their remains, the locality being replaced by fibrous tissue. The destruction occurs only with certain doses and begins at once. Small doses are followed by an increase in lymphocytes. The myeloid cells are affected only by heavier radiation, and the changes take place only after some time. This can be observed clinically when, after heavy doses, some days elapse before there is a drop in the number of neutrophils. Later observations by Aubertin,[3] Schinz, Mottran and others indicate a destruction of myelocytes of the neutrophilic series, but no material change in the eosinophilic and basophilic series. Schisler and Brown [4] observed a relative rise in the number of neutrophils when myelocytes were destroyed. They were studying myeloid leukemia and found that the total number of neutrophils was reduced more than the percentage. Aubertin's [3] work indicates that regeneration of neutrophils is manifested by the appearance of young cells, as indicated by the Arneth formula. He showed, however, that all marrow cells were less sensitive than splenic cells, and he and others have shown that the lymphatic tissues feel the effect of the roentgen ray sooner than do marrow tissues, but that the effect passes off sooner. In general it may be said that under pathologic conditions the cell to feel the effect first is the young stage of the variety that is abnormally active. Radium has more effect on the marrow than does roentgen ray, but the nature of the effect is essentially the same—a reduction in the number of myelocytes and of polymorphonuclears but with the latter relatively more numerous.

The effect of radiation on the marrow is further shown by the low percentage of neutrophils in roentgenologists and the aplastic anemia that is sometimes observed in them.

There are few direct references in the literature to the changes of lymphatic cells in myeloid leukemia or of neutrophils in lymphatic leukemia. They tend to show a reduction of the number of lymphocytes in myeloid leukemia without disturbance of their percentage. Stengel and Pancoast,[5] in 1912, warned against treating patients who showed a

2. Heineke: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **14**:21, 1905; München. med. Wchnschr. **50**:2090, 1903; ibid. **51**:785, 1904; Deutsche Ztschr. f. Chir. **78**: 196, 1905.

3. Aubertin: Compt. rend. Soc. de biol. **58**:417, 1905; ibid. **54**:410, 1908; Arch. de méd. expér. et d'anat. path. **20**:273, 1908.

4. Schisler and Brown: M. Record **99**:505, 1921.

5. Stengel, Alfred, and Pancoast, H. K.: The Treatment of Leukemia and Pseudoleukemia with X-Rays, J. A. M. A. **59**:1166 (Sept. 28) 1912.

rapid and marked drop in the number of circulating leukocytes. Soiland [6] also discussed this, and he and others note the danger of driving the figures for leukocytes down to below normal. The best practice seems to dictate stopping the treatment just before normal figures are reached. When in myeloid leukemia there is a relative rise in the number of myelocytes with a fall in that of the total leukocytes, a fatal outcome may be expected. This suggests that the effect of radiation on acute leukemia is dangerous to the extent that young cells are forced to degenerate.

Doubtless, therefore, radiation can reduce the production of the leukocytes of the two principal varieties. I have tried to show in my cases that the large mononuclears were altered in some definite way, but without success. The number of eosinophils tends to rise in some and to fall in others, but there was not any regularity.

Despite the control by radiation of cellular overproduction and the clinical improvement in most cases by such treatment, there is not any evidence that the formative cells are made to behave themselves and to produce the normal cells in normal numbers. Nägeli, in his textbook, writes of an improvement of cytogenesis without explaining its operation; this is open to question. On the contrary certain cases of all varieties of leukemia tend to reach a resistant stage at which a favorable change cannot be effected. Radiation, however, can be shown to drive down useful cells, and at present there is not any selective method.

I shall now discuss the cases on which the present study is based. The figures for the blood counts are illustrated in charts, the plan of which demands some elucidation. The curves are based on the blood counts as made under clinical conditions. The intervals are not regular nor are they the same in all the cases. Nevertheless, the course of blood pictures can be followed, and, accepting the diagnoses as correctly made on the criteria given before, these graphs portray rather definite features of the neutrophil number and reaction during treatment. They can also be read to support the lessons that are conservatively drawn from them.

The curves are made on the number, not the percentage, of circulating leukocytes, lymphocytes and neutrophils. At the lower left corner of the charts, in appropriately shaded spaces, are shown the normal limits of each of the three groups. (A calculation of the exact number of cells should be made oftener in all kinds of cases. When the total is abnormal, one usually fails to realize the exact number of each of the varieties.) The figures given, from 7,000 to 8,000 total leukocytes, from 4,600 to 5,200 neutrophils and from 1,600 to 2,200 lymphocytes,

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6. Soiland: Southwestern Med. **6**:196, 1922; Ann. Med. **1**:405, 1920; J. Radiol. **2**:25, 1921.

are averages from several acceptable authors.[7] Because of the variation of totals, every chart cannot be made on the same scale, it being obviously impossible to illustrate conveniently on the same scale of drawing a leukocyte number of 300,000 and one of 5,000. The basis of all is, however, the same, so that the reader can quickly become familiar with the method. Heavy solid lines indicate neutrophils, dash lines lymphocytes and light lines total leukocytes. The black squares indicate death.

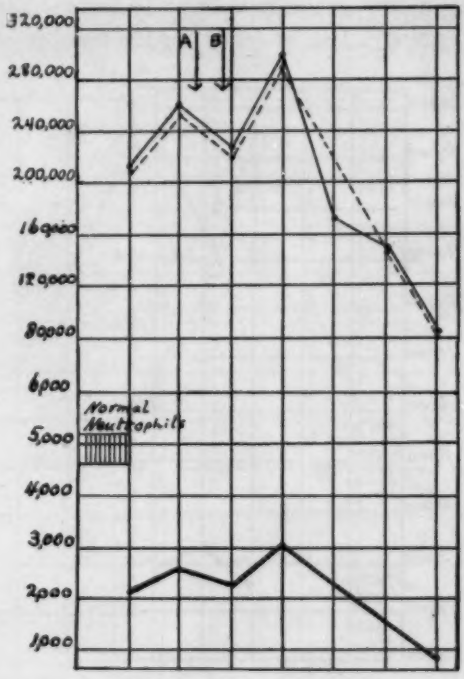

Chart 1 (case 1).—An example of typical chronic lymphatic leukemia, clinically and from the blood picture, nine weeks' observation; the patient had a decided secondary anemia; the participation of the polynuclear cells in the inactivity of the bone marrow may be noted; during the course of radiation treatment the neutrophils tended to fall, their number following the course of the total and lymphocyte counts; transfusion was necessary; at all times the neutrophils were below the normal number; *A* indicates transfusion; *B*, roentgen ray begun. In this and the following charts, the heavy lines indicate neutrophils; the dash lines, lymphocytes; the light lines, total leukocytes, and the black squares, death.

7. These modes are the ones in common use. Some recent work by Sabin et al. (Bull. Johns Hopkins Hosp. **37**:14, 1925) and by Shaw (J. Path. & Bact. **30**:1, 1927) would indicate that the range may be much greater, and that during twenty-four hours a variation of considerable degree may take place normally. This fact, however, does not vitiate the results of this work, because the course of the neutrophils rather than any single count is the essential feature.

The first two graphs illustrate two cases of chronic lymphatic leukemia. The total and lymphocyte counts were influenced as expected by radiation. The number of neutrophils was below normal and the effect of the roentgen ray was to keep it there or to drive it lower. The number of polymorphonuclears in chronic lymphatic leukemia has long been known as low, but this has not been emphasized; Nägeli, in his textbook on the blood, does not mention it. In none of these cases did it reach normal at any time.

Case 3 was one of low grade lymphatic leukemia that had a suggestively infectious etiology. The tendency for the number of neutrophils

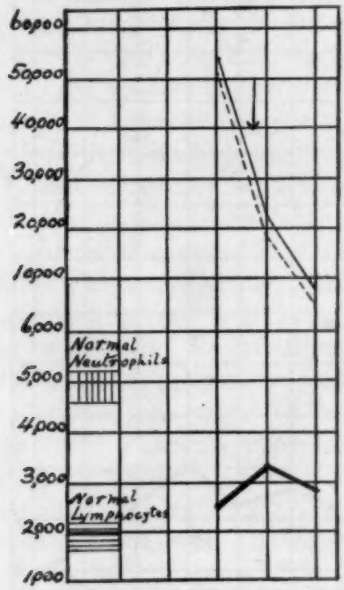

Chart 2 (case 2).—A case of chronic lymphatic leukemia in which radiation gave fairly good results; one week's observation; the records show only the proportionately low number of neutrophils; the patient reacted well but has had a return and recently had another series of roentgen-ray treatments which are not included; the neutrophils remain low; the arrow indicates roentgen-ray treatment.

to fall all through the course is evident; dips in the count can be seen to follow nearly every exposure to the roentgen ray.

Case 4 is definitely a sublymphemic leukemia with subnormal neutrophils.

The next three cases, 5, 6 and 7, are instances of aleukemic adenoses. In case 5, the neutrophils were constantly low in number, and were affected at one time by the roentgen ray. This was just before pneumonia developed, and one may suspect the relationship between this

low count and susceptibility to infection. This case, because of the low number of neutrophils and their sensitivity, is one of the borderline cases to which Pinkus has called attention as a possible relative of true leukemia. Cases 6 and 7 show neutrophils that try to remain within normal counts and lymphocytes that fall in number progressively with radiation.

Case 8, one of marked lymphadenopathy with leukopenia and greatly reduced neutrophils, is one that was not helped by radiation. Perhaps this was a case of acute aplasia of the marrow and in which the number of lymphocytes was increased, as the neutrophils failed.

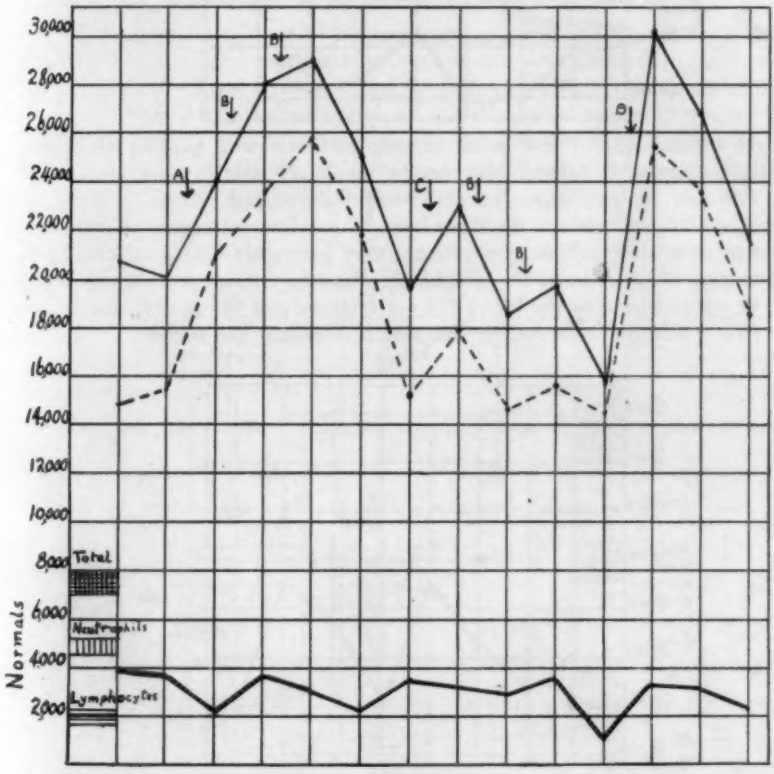

Chart 3 (case 3).—A low grade lymphatic leukemia of chronic character, which was never satisfactorily explained on a clinical basis; five weeks' observation; apparently a low grade infection, of pulmonary origin, in which the lymphocytes were stimulated and the neutrophils depressed; the neutrophils tended to fall (heavy line), and a drop occurred after nearly every roentgen-ray exposure, until they were finally stopped when the number of cells fell to 1,200 per cubic millimeter; vaccine and bath therapy did not raise the number of these cells; the number was always below normal; the case certainly belongs near the chronic lymphatic leukemias; *A* indicates roentgen ray begun; *B*, roentgen ray; *C*, vaccine; *D*, roentgen ray stopped.

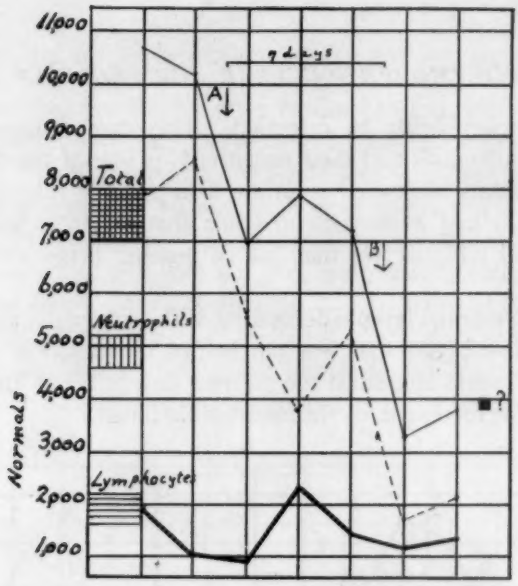

Chart 4 (case 4).—A low grade chronic leukemia with general adenopathy and slightly enlarged spleen, with severe secondary anemia and low platelet count (chronic sublymphemic leukemia—thrombocytopenic anemia); three and one-half weeks' observation; the depression of marrow activity is shown in the number of circulating polymorphonuclears; they were unfavorably affected by the roentgen ray, which reduced the lymphocyte count to normal proportions; radiation was stopped because the blood did not improve and the patient was in poor condition; *A* indicates roentgen ray started; *B*, roentgen ray stopped.

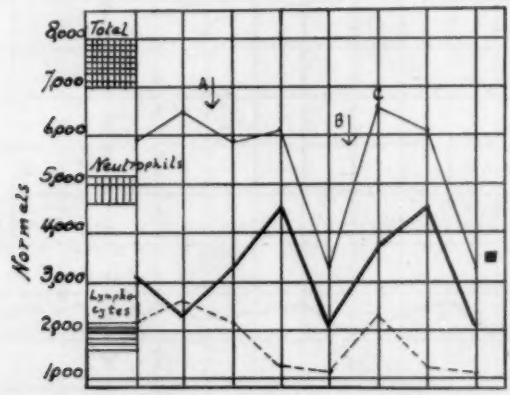

Chart 5 (case 5).—A case of generalized lymphadenopathy in which the relations of the total leukocytes, neutrophils and lymphocytes remained about normal, but the total numbers were subnormal in most of the course (aleukemic lymphadenosis); six weeks' observation; the neutrophils were variable and did not show the effect of the roentgen ray so much as did the lymphocytes; they were obviously unable to cope with the pneumonia when it developed; autopsy confirmed the diagnosis showing a picture of lymphatic leukemia with the addition of large masses of leukemic tumors in the retroperitoneal area; the bone marrow was not studied; if this were to be included with the chronic lymphatic leukemias, it would have to be considered as being studied during an interval when the relations of the important white cells were other than usual for the chronic form of the disease; *A* indicates roentgen ray started; *B*, roentgen ray stopped; *C*, pneumonia.

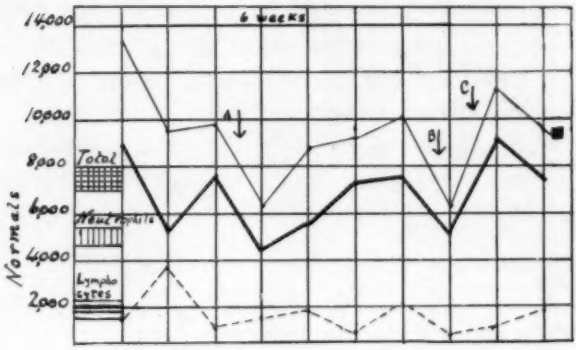

Chart 6 (case 6).—A case of generalized lymphadenopathy without involvement of the spleen and without leukocytosis; the neutrophil count was slightly affected by the radiation treatment; the red cells and hemoglobin remained normal to the end; the last phase consisted of multiple bone tumors that were called myeloma because of the structure of one that was removed at a limited autopsy; the diagnosis was confirmed at autopsy; *A* indicates roentgen ray began; *B*, roentgen ray stopped; *C*, interval-bone tumors.

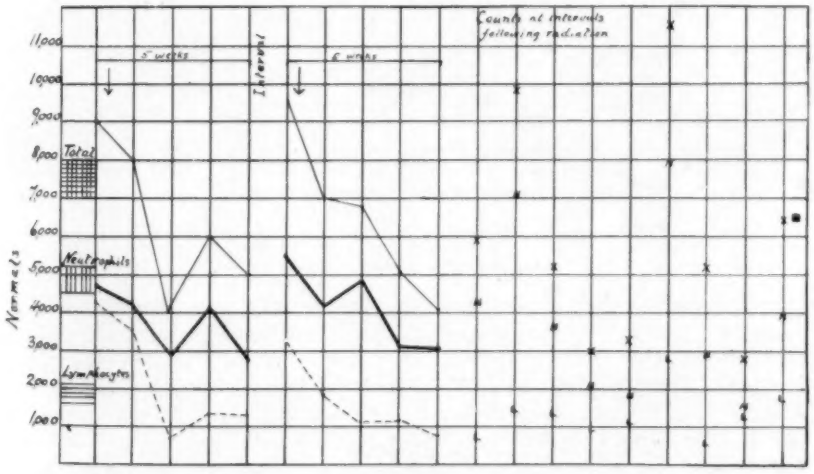

Chart 7 (case 7).—A case of aleukemic lymphadenopathy with a slightly disproportionate lymphocytosis; the lymphocytes were apparently susceptible to the roentgen ray, the neutrophils much less so; this case showed decided lymphadenopathy, with enlargement of the spleen and liver; the whole observation covered two years; the primary growth started in the neck and spread thence to the mediastinum and axillae, and then the abdomen; blood counts would indicate that at no time did the patient have a leukemia; the terminal picture was that of multiple myeloma; a review of this case seemed to indicate that it was a slowly progressive lymphosarcomatosis; arrows indicate roentgen-ray series.

Case 9 is an example of leukosarcoma with susceptible neutrophils.

Cases 10, 11 and 12 are examples of lymphosarcoma in which the neutrophils were practically always within expectable variations and showed only transient radiation effects.

In the average Hodgkin's cases in the early and middle stages, the neutrophils, while varying slightly with the total count, remain mostly above normal. They are not driven to subnormal levels.

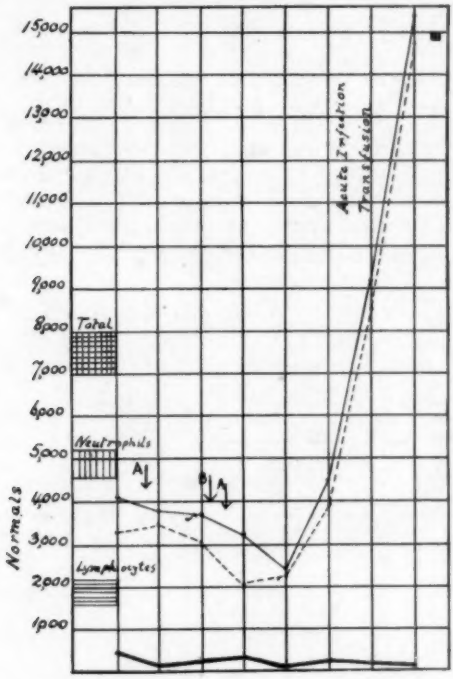

Chart 8 (case 8).—A case of general lymphadenopathy with slow failure of bone marrow activity; nine weeks' observation; it may be noted the neutrophils were hardly ever more than one tenth of their normal number; the red cells fell in nine weeks from 4,000,000 to 2,500,000 and the hemoglobin from 75 to 50 per cent; during the course of radiation treatment the glands decreased and practically disappeared and the man became much worse; despite transfusions the condition of the blood did not improve; when an acute respiratory tract infection appeared, the neutrophils did not respond, the rapid rise in circulating leukocytes being entirely due to small mononuclears; autopsy was not performed; *A* indicates roentgen ray; *B*, transfusion.

A case of nonlymphoid sarcoma did not show any susceptibility of neutrophils in the first series, while the second series occurred late in cachexia.

Endothelioma also failed to be distinguished by a special neutrophil number or susceptibility.

SUMMARY

The lack of wisdom in drawing conclusions from any present knowledge of lymphadenopathies is only too evident, but it would seem that a little further support may be had, from the analysis of neutrophils and their reaction to radiation, for the separation of certain groups and for rules of treatment.

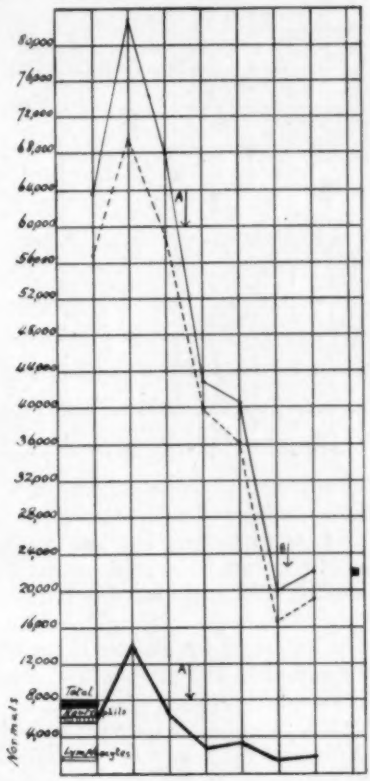

Chart 9 (case 9).—A case of tumor of the mediastinum and abdomen with insignificant enlargement of lymph nodes; five weeks' observation; the mass in the chest was accompanied by considerable fluid; the abdomen was as large as in a full term pregnancy, only part of which enlargement was fluid; the circulating cells were chiefly adult small lymphocytes; there is evidently a leukemia; this case therefore comes in the group classified as leukosarcoma; it may be noted that the neutrophil count was normal or above until roentgen-ray treatment was started, when it fell to low figures; the patient died after a bronchopneumonia; the neutrophils did not increase during this infection; *A* indicates roentgen ray begun; *B*, roentgen ray stopped.

From the evidence collected here the leukemic group is composed of true chronic lymphatic leukemia, sublymphemic leukemia and leukosarcoma in that they have, with lymphocytosis, a low number of neutrophils that are very susceptible to radiation treatment. In aleu-

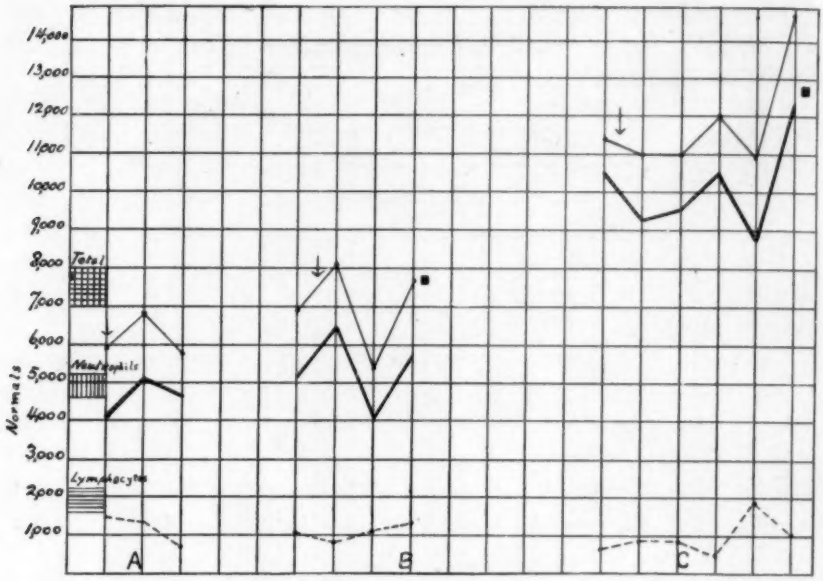

Chart 10.—Arrows indicate roentgen-ray series. *A* (case 10), was diagnosed as lymphosarcoma or possibly aleukemic lymphadenosis, of two years' duration, originating in the neck and extending to the chest, and finally to the lower trunk as retroperitoneal and pelvic tumors; three weeks' observation; the blood count during one of the patient's admissions to the hospital is shown; almost identical figures occurred on another admission; the neutrophils were practically unaffected by the roentgen-ray series and the counts were within normal limits. *B* (case 11), lymphosarcoma of the neck occurring five years after removal of tumor from the neck, five weeks' observation; the final picture was that of lymphosarcomatosis, which was confirmed by autopsy; the counts were made during the final admission and show that the radiation did not have a marked effect on the neutrophils, certainly not keeping them below the normal line. *C* (case 12), five months' duration, apparently beginning as a tumor of the groin after injury, thence extending to the axilla and to the neck, followed later by signs of growth in the chest; three and one-half weeks' observation; diagnosed as lymphosarcoma because of the picture of excised glands, the blood count and the rapidity of the process; autopsy revealed a large mediastinal growth, isolated nodules in the spleen and kidney and a large mass in the retroperitoneal and iliac region; the blood showed a moderately high leukocyte count with a relatively high neutrophil number; the neutrophils were unaffected by the primary process and not materially reduced if at all by the roentgen ray.

kemic lymphadenosis the percentages and numbers of neutrophils and lymphocytes tend to approach normal with relative insusceptibility to radiation. The cases have a tendency to osseous involvement, which was not attended by polynucleosis, however, in my two cases, and therefore suggest myeloma which is not characterized by a peculiar blood picture. This group of adenoses somewhat resembles lymphosarcoma in hematology. The tendency to final malignant stages in adenosis, as evidenced by the bony tumors, increases the resemblance. The neutrophils in lymphosarcoma do not decrease consistently under radiation.

Hodgkin's disease is marked by a polynucleosis which is indifferent to radiation except in the malignant and febrile cases in which these cells are variable. In my single cases of reticulum cell sarcoma and endothelioma the neutrophils were unaffected by radiation and of no definite numbers.

From these figures, then, one can deduce that there is a leukemic group, true chronic leukemia, sublymphemic leukemia and leukosarcoma, and a sarcoma group, aleukemic lymphadenosis and lymphosarcoma, with distinct neutrophil picture and reaction to radiation. These are separate from Hodgkin's disease, which varies with its type, and from endothelioma and nonlymphoid sarcoma. These features, if corroborated, will with a biopsy, somewhat simplify the classification of a given case.

Laboratory Methods and Technical Notes

QUICK CELLOIDIN METHOD FOR PREPARING TISSUES

B. W. Rhamy, M.D., Fort Wayne, Ind.

In the routine examination of tissues for diagnosis, an important feature is the time required before a report may be made. In a large percentage of cases, the physician wants a prompt report. Some laboratories are preparing all of their sections by the freezing method, making possible reports by mail twenty-four hours after the material is received. There are, however, certain limitations to the frozen section method that make further steps advisable for a complete study. The logical procedure would be (*a*) to employ the frozen section method in urgent cases, to be followed, if advisable, by one of the more elaborate embedding methods, and (*b*) to use the embedding methods in all cases in which an immediate report is not required.

In the latter case, it follows that if a satisfactory method of preparing sections is employed, then for economic reasons, the less time consumed, the better. In regard to the use of paraffin and celloidin, each has its advantages and disadvantages, and the use of either is largely a matter of choice. Paraffin has been used the most, largely because sections can be made in a few hours if acetone and benzene are used, while the celloidin method takes at least five days. The objections to the use of paraffin are: (1) Sections must be affixed to slides before staining; (2) the paraffin sections fold, curl and crinkle; (3) if too hard, they break; (4) small pieces of tissue must be used.

On the other hand, with the use of celloidin, there is no limit to the size or consistency of the tissue sectioned. While with the use of paraffin such hard tissues as muscle or skin are cut with difficulty, celloidin sections of any tissue can be made equally well. The chief objection to celloidin, then, is the time consumed. To offset this disadvantage, I offer the following quick method of preparing celloidin sections. I have used it for some time and so far, I have not found any objectionable features. This method enables one to prepare a report on a celloidin section in forty-eight hours. The preliminary formalin is to fix the tissue framework, thereby preventing undue shrinking by the acetone. The quantity of acetone should be about twenty times the volume of the tissue.

METHOD

1. Ten per cent formalin, 10 minutes.
2. Acetone (depending on size of tissue block), two changes, from ½ to 2 hours.
3. Acetone, absolute alcohol, ether, equal parts, from ½ to 2 hours.
4. Acetone, 1 part, thin celloidin, 3 parts, from ½ to 2 hours.
5. Thick celloidin, 24 hours.
6. Mount and harden in full strength denatured alcohol.

After step 3, the method may be varied thus, if desired:

4. Absolute alcohol, ether, equal parts, from ½ to 2 hours.
5. Thin celloidin, from ½ to 2 hours.
6. Thick celloidin, 24 hours.

A SIMPLE METHOD FOR STAINING RETICULUM*

ETHEL MAY KINNEY, SC.D., CHICAGO

While alkaloidal reagents were being tested, in an endeavor to crystallize ingested morphine in the tissues of morphinized rats, it was discovered that tissues treated with sodium sulphantimonate in solution of formaldehyde were stained selectively for reticulum.

This solution, which simultaneously fixes the tissue and stains the block for reticulum, is prepared by adding 1 Gm. of sodium sulphantimonate to

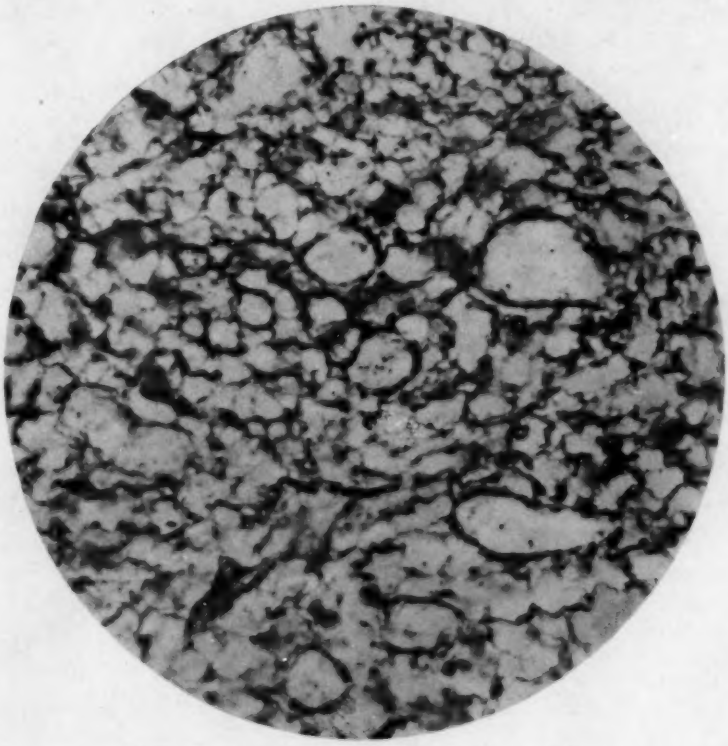

Fig. 1.—Reticulum of splenic pulp; × 560.

100 cc. of 4 per cent formaldehyde immediately before using. The tissue should be cut only a few millimeters thick and for the best results should be fresh, although material which has been removed at autopsy several hours after death has been successfully stained by this method.

When this 1 per cent solution is to be used, the tissue should be removed after about eighteen hours. The fixing time may be shortened by from nine to twelve hours if a 1.5 per cent solution is used. In either case, however, the tissue should be removed at the end of the stated time, as the stain then

*From the Leon Klein Fund of the Michael Reese Hospital and the Nelson Morris Institute for Medical Research.

seems to begin to disappear. The tissue is then treated as any other material which is to be embedded in paraffin, with the exception that it cannot be left in the clearing agent more than from one to two hours, whether xylene or cedar oil is used. The stain completely disappears if the material is left in cedar oil for as long as twelve hours. The stain is stabile in alcohol, and the tissue may remain in 70 per cent alcohol as long as desired.

After the sections are cut and mounted in the usual manner, the paraffin is removed with xylene and the cover slip immediately attached with neutral balsam.

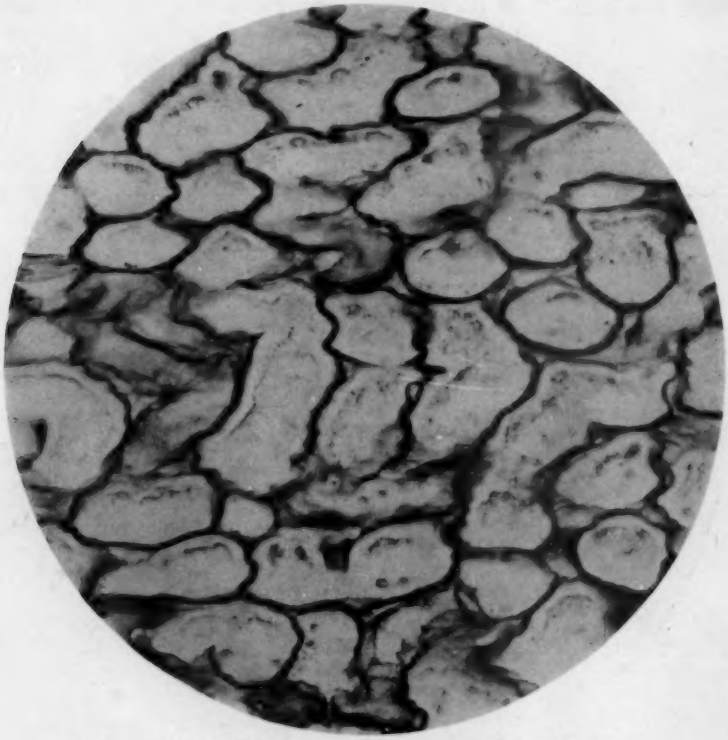

Fig. 2.—Intertubular reticulum of renal cortex; × 320.

By this method the reticulum is stained a dark brown and other connective tissue, yellow. An occasional nucleus may be stained. The remainder of the tissue is unaffected by this method and may be stained for routine observation by any of the ordinary stains, such as hematoxylin and eosin. However, hematoxylin or other basic stains obscure the reticulum.

The stain resembles other reticulum stains in that it does not penetrate deeply and is somewhat patchy, especially in the spleen. Other organs, such as the kidney and pancreas, stain more evenly.

This method offers advantages over the present methods in use in that it is exceedingly easy to perform, it works well on material obtained at autopsy, and the stained material is suitable for counterstaining for routine observation.

General Review

THE PATHOLOGIC ANATOMY OF INFLUENZA

BASED CHIEFLY ON AMERICAN AND BRITISH SOURCES*

EUGENE L. OPIE, M.D.
PHILADELPHIA

The increasing prevalence of respiratory disease in camps of the United States Army became evident during 1917 and 1918 before the great epidemic of influenza and was the subject of investigation directed by the office of the Surgeon General. Numerous studies of the bacteriology and the pathology of pneumonia following influenza were made by American and British observers during the epidemic of the fall of 1918, and subsequently several monographs devoted to the subject were published. The present review is limited to articles published in English because the literature on the subject in other languages has been collected elsewhere in the ARCHIVES. The bacteriology of influenza will be considered only in its relation to the pathologic anatomy of the disease.

Observations during the epidemic of 1918 failed to prove that *B. influenzae* of Pfeiffer is the cause of influenza. The agent concerned produces changes in the respiratory tract that in most instances pursue a benign course. When death occurs there is invariably severe infection of the bronchi and lungs by other bacteria as well. Influenza evidently renders the respiratory passages susceptible to invasion by a considerable variety of micro-organisms, and the injury it causes to the respiratory mucous membranes doubtless has an important part in diminishing resistance to invasion. The presence of virulent micro-organisms, e.g., hemolytic streptococci, in the environment of the patient is a determining factor in the occurrence of fatal infection.

Many have thought that the leukopenia of influenza lowers the resistance of the patient to bacterial infection. The leukocyte count is often less than 5,000 (Keegan), and the absolute count of polymorphonuclear leukocytes is diminished (Bloomfield and Harrop, Bunting and others). Even when pneumonia occurs leukocytosis is usually slight or nil (Blanton and Irons; Brem, Bolling and Casper; Lucke, Wight and Kime, and others).

Changes in the mucous membrane of the mouth and pharynx which are well developed after the first twenty-four hours following the onset

* From the Henry Phipps Institute, University of Pennsylvania.

of influenza have been described by Bloomfield and Harrop. The pharynx, tonsils, pillars and soft palate become vermilion or scarlet, and often erythema extends over the entire mouth. Minute hemorrhagic spots are seen on the mucosa inside of the cheeks and occasionally on the gums, soft palate, mucous borders of the lips and uvula. Swelling of lymphoid tissue produces corrugation of the posterior pharyngeal wall.

Infection of the accessory nasal sinuses appears to be an almost invariable accompaniment of influenzal pneumonia. In twenty examinations made by Abrahams, Hallows and French, they were found to be normal only once. Bright yellow pus usually filled the sphenoidal sinus, but occasionally there was turbid serous fluid and the membrane was deep red. In twenty autopsies on those who had died following influenza, Wolbach examined the sinuses and found infection in the sphenoidal sinus in all, in the frontal sinus in seven and in the ethmoidal sinus in eight; infection of the middle ear occurred thirteen times. *B. influenzae* with pneumococcus or streptococcus were grown from the contents of the sinuses. Similar observations have been made by Stone and Swift and by Lucke, Wight and Kime. In fourteen of sixty-five autopsies performed, the latter found the mastoid cells infected on one or both sides, but necrosis of the bone was not present.

Changes in the trachea (Klotz) and larger bronchi seen when fatal pneumonia has followed influenza are such as might favor the penetration of bacteria into the lower respiratory passages (Winternitz, Wason and McNamara; Opie, Blake, Small and Rivers). The mucosa is intensely injected, and there is superficial ulceration. In the larger bronchi there is occasionally necrosis of epithelium from the cells of which, although their architecture is preserved, the nuclei have disappeared, and loss of the injured epithelium occurs. Changes are almost invariably found in the mucous glands; the ducts and acini are often distended with mucus, the cells of the acini undergo necrosis and lymphoid and plasma cells accumulate about the ducts and acini.

Profound changes in the smaller bronchi are perhaps the most characteristic feature of influenzal pneumonia. In some patients who recover from influenza, bronchitis may be unaccompanied by any evidence of pneumonia, and with fatal pneumonia in one part of the lung small bronchi elsewhere may contain viscid, mucopurulent exudate although the surrounding lung tissue is free from pneumonic consolidation (purulent bronchitis, capillary bronchitis). In these instances, the small bronchi and bronchioles contain polymorphonuclear leukocytes in abundance whereas the alveolar ducts, alveolar sacs and tributary alveoli contain air. The lung tissue is often distended and fails to collapse when cut (acute bronchitic emphysema described by Torrey and Grosch).

With influenzal pneumonia changes in the small bronchi, especially those which do not contain any cartilage in their walls, may vary from superficial necrosis of the mucosa to complete destruction of the bronchial wall, so that the bronchus is replaced by a small abscess surrounded by consolidated alveolar tissue. Various degrees of injury are inflicted on small bronchi, namely, necrosis penetrating a variable distance into the bronchial wall and occasionally extending to adjacent alveolar tissue, peribronchial hemorrhage or peribronchial pneumonia in a zone encircling the bronchus, presumably due to direct extension of the injurious agent through the bronchial wall, and bronchiectasis.

CLASSIFICATION OF INFLUENZAL PNEUMONIA

Those who have studied the pathologic process of pneumonia following influenza have recognized the anomalous character and variety of the lesions that occur.

Winternitz and his co-workers regard any classification of such cases of pneumonia as unsatisfactory, but they divide their cases into the following groups: (1) an acute diffuse fulminating type of pneumonia, (2) pneumonia with necrosis and (3) pneumonia with organization.

A committee appointed to investigate influenza in the British armies in France found bronchopneumonia in fifty-four autopsies, confluent bronchopneumonia in eleven, bronchiolitis or miliary pneumonia in five, purulent bronchitis with little, if any, consolidation in twenty-six and lobar pneumonia in six. In sixty-one autopsies, Medalia found bronchopneumonia fifty-six times and lobar pneumonia five times; Lucke, Wight and Kime found seven instances of lobar pneumonia alone and six instances of lobar pneumonia with bronchopneumonia in 126 autopsies on persons who had died following influenza.

An attempt to classify influenzal pneumonia by the etiologic agent presumably concerned in its production has been made by Mac Callum: (*a*) When pneumonia following influenza is caused by the pneumococcus, the lungs contain bloody fluid in great quantity and the consolidation is lobular in distribution, but tends to become confluent. Alveolar ducts are widely dilated, contain few polymorphonuclear leukocytes and are often lined with a layer of hyaline material. This type has been designated by some observers as acute fulminating pneumonia, and Wolbach and Klotz found evidence that it was caused by Pfeiffer's bacillus. (*b*) Staphylococcal pneumonia doubtless occurs, but Mac Callum did not find any definitely recognizable instance of the lesion. (*c*) Streptococcal pneumonia was accompanied by lobular consolidation, and bronchi and alveoli contained streptococci in great number. Wide areas of lung tissue had undergone necrosis. Lymphatics were distended and contained streptococci, and interlobular septums were edematous,

but Mac Callum did not find the interstitial pneumonia caused by hemolytic streptococci following influenza that he had found following measles. (*d*) In pneumonia caused by *B. influenzae* of Pfeiffer, Mac Callum says the bronchi contain thick purulent exudate in which this micro-organism is abundant. In two instances, it was recovered in pure culture. Palpable shotlike, grayish-yellow nodules were thickly scattered in the substance of the lung. The walls of the bronchi were infiltrated by mononuclear cells, and there was new formation of fibrous tissue. The walls of the alveoli were thickened, and the alveoli often contained fibrin in process of organization. The lesion had all the characters of the pneumonia that he had previously found after measles and attributed to the hemolytic streptococcus except for the absence of conspicuous changes in the lymphatics, absence of intense pleural infection and the relatively smaller number of polymorphonuclear leukocytes.

The United States Army commission assigned to Camp Pike (Opie, Freeman, Blake, Small and Rivers) had an unusual opportunity to study the entire course of an epidemic occurring among 50,000 troops and to examine those who died during the following two months from pneumonia acquired during the epidemic. Autopsies were performed on 228 adults who died as the result of pneumonia following influenza, and bacteriologic examinations were made of the bronchial content, lung tissue and blood of the heart. Pneumococci were present in the bronchi and in the consolidated lung tissue in about half of all cases, and in slightly more than one third they had penetrated into the blood stream, thus doubtless having had an important part in causing death. Almost identical figures described the distribution of the hemolytic streptococcus after death. In contrast with these micro-organisms, the bacillus of Pfeiffer was found in the bronchi in approximately 80 per cent of the autopsies, in the consolidated lung tissue in 46 per cent and only once in the heart blood. It is evident that pneumococci and hemolytic streptococci pass readily from bronchi to lung tissue and, as death approaches, into the blood stream, whereas the bacillus of Pfeiffer, although usually, if not always, found in the bronchi, is far less frequently recoverable from pneumonic lung tissue, and even then is perhaps lodged in the small bronchi. The bacillus certainly had had a part in the production of bronchitis following influenza, but was so seldom obtained in pure culture from bronchi (three instances) or lung (one instance) in these autopsies that it may be regarded as one of many micro-organisms invading the lower respiratory passages. Lobar pneumonia caused, with few if any exceptions, by the pneumococcus was found sixty-four times, lobar and bronchopneumonia in the same lungs thirty-four times and bronchopneumonia without suppuration eighty times. In these instances of lobar pneumonia and bronchopneumonia, there was often secondary infection with the hemolytic streptococcus

but no suppuration. Suppurative pneumonia accompanying bronchopneumonia occurred as follows: Abscess and necrosis (almost invariably caused by the hemolytic streptococcus) in thirty-six autopsies, interstitial suppuration (caused by hemolytic streptococcus) in twenty-one autopsies and staphylococcus abscess in six.

In minor epidemics which have followed the pandemic of 1918, changes in the lungs described by Meleney and Pappenheim and by Symmers, Dinnerstein and Frost do not seem to have differed from those seen during the great epidemic.

Minor outbreaks of fatal pneumonia following measles in United States Army camps preceded the great epidemic of influenza in the fall of 1918. Before this pandemic, the existence of influenza in the camps was scarcely recognized. Mac Callum, who has given special attention to hemolytic streptococcus pneumonia of measles, makes the suggestion that influenza may have been associated with measles in the production of secondary streptococcus infections. Among eighteen autopsies performed on patients who died of pneumonia following measles during or shortly after the epidemic of influenza, all of the lesions regarded as characteristic of influenzal pneumonia were found by Opie, Blake, Small and Rivers. There were, in association with profound injuries to bronchi, lobar pneumonia, peribronchiolar pneumonia, which was in some instances hemorrhagic, suppurative pneumonia of characteristic type due to the hemolytic streptococcus, unresolved or organizing pneumonia and bronchiectasis. These observations support the opinion that influenza attacking patients with measles had a part in the production of pneumonia.

BRONCHOPNEUMONIA

Severe injury to bronchi, often with conspicuous evidence of bronchitis, is constantly found when death has followed influenza, and in most instances, the associated patches of consolidation are clearly grouped about small bronchi. The varied character of pneumonia following influenza is due to the occurrence of the following types of consolidation in numerous combinations:

Lobular Consolidation.—This type of consolidation often implicates a large part of the substance of the lung (pseudolobar). In persons who die within a few days after the onset of pneumonia, the consolidated lung tissue is flaccid, red and edematous (the acute diffuse type of Winternitz, early stage of Klotz), but in other instances the lobular consolidation is firmer and gray (secondary stage of Klotz).

Peribronchiolar Consolidation.—Peribronchiolar consolidation is limited to the alveoli and alveolar ducts immediately about bronchioles. Small nodules (fig. 2 of Opie, Blake, Small and Rivers) of consolidation are widely scattered in the substance of the lung (the miliary broncho-

pneumonia of English writers). The lesion is the earliest stage of what MacCallum has designated interstitial pneumonia, but distinctive changes in interstitial tissue occur only when the disease pursues a chronic course.

Hemorrhagic Peribronchiolar Consolidation.—This type of consolidation occurs as gray spots about bronchioles seen on a deep red background formed by hemorrhagic exudate within the intervening alveoli and alveolar sacs. Pfeiffer regarded the lesion as characteristic of influenza.

Peribronchial Consolidation.—A zone of alveoli encircling small bronchi is affected in this type of consolidation and suggests that the agent producing the lesion has penetrated the wall of the bronchus and entered the surrounding lung tissue (Opie, Blake, Small and Rivers).

Unresolved or organizing bronchopneumonia is associated with organization of the pneumonic exudate and may occur in consolidated lung tissue in any of the foregoing situations, so that new fibrous tissue may be formed about bronchi and blood vessels, in interalveolar walls and in interlobular septums. The lesion is invariably accompanied by purulent bronchitis and usually by bronchiectasis. The lungs are distended and do not collapse even when cut. Particularly characteristic are indurated foci of peribronchiolar pneumonia, which, being firm and sharply defined as the result of organization of the exudate, may have the appearance of tubercles (miliary bronchopneumonia).

The combinations in which these forms of consolidation occur are so varied that the attempt to classify the affected lungs by the predominant type of consolidation is futile. Nevertheless, it is desirable to discuss in more detail those changes that have attracted most attention.

Acute or "Fulminating" Influenzal Pneumonia.—This type of pneumonia has been recognized by all of those who have studied the pathologic anatomy of the disease. At autopsy the lungs are largely airless and distended with bloody serous fluid which is in the alveoli, bronchi, interstitial tissue and below the pleura. The opinion that this form of pneumonia rapidly overwhelms those who are attacked is apparently based on the characters of the lesion found after death, for in forty-four instances studied by Winternitz and his co-workers the average duration of the illness was nine days. Lyon gives the average duration as 7.7 days and Nuzum, Pilot, Stangl and Bonar cite eight cases in which the course of the disease was from three to five days. Bradbury and Krumbhaar saw this type of disease as early as the fifth and as late as the twentieth day after the onset.

The lungs are large and heavy, and the pleural surfaces are mottled with brilliant colors (well shown in the excellent plates of Winternitz, Wason and McNamara). Small bright red hemorrhages occur and

larger brown patches are due to accumulation of blood stained fluid below the pleura (Le Count). Violet or purple areas, often limited by lobule boundaries, are largest over the lower two thirds of the lung and overlie lung tissue which is partially consolidated. Between the deeply colored parts are pale pink areas containing air. Interstitial tissue between secondary lobules is edematous; lymphatics are distended and lymph nodes at the hilum of the lung are enlarged and succulent.

The alveoli contain red blood corpuscles in varying abundance within a network of fibrin. Hemorrhage into the alveolar tissue may resemble an infarct (Klotz; see plate I of Sundell). Polymorphonuclear leukocytes are absent or few in number, and bacteria, singly, in pairs, clumps and chains are often seen free in the fluid. Winternitz, Wason and McNamara have directed attention to the aplastic character of the exudate in this form of pneumonia. They suggest that the lack of polymorphonuclear reaction may accompany the suspension of the formation of leukocytes, causing both leukopenia and impaired local inflammatory reaction.

The formation of a layer of hyaline material on the inner surface of alveolar ducts and infundibula has been described by many writers (Le Count, Goodpasture and Burnett, Wolbach and others). Wolbach regarded it as a distinctive character of influenzal pneumonia, but Brannan and Goodpasture have described two cases in which the change occurred without influenza. This hyaline material may form a continuous layer resting on the wall of the alveolar duct and extending across the orifices of the tributary alveoli, and may be found similarly placed within alveolar sacs. It has the appearance of coalescing strands of fibrin, but Goodpasture believes that it consists in part of fused necrotic mononuclear cells. It does not give the staining reactions of fibrin (Klotz, Mac Callum), but it is not improbable that these reactions have been lost, for, as Brannan and Goodpasture point out, hyaline fibrin of diphtheritic exudate does not retain the peculiar reactions of fibrin. This uninterrupted layer sometimes surrounds a bubble of air, but more frequently it encloses serum in which a few red blood corpuscles are suspended, although leukocytes and fibrin are abundant in the adjacent alveoli. Wolbach and Opie, Blake, Small and Rivers have offered the suggestion that this hyaline material is a conspicuous layer of fibrin formed when a bubble of air is drawn by inspiration into an alveolar duct or into an alveolar sac containing a fibrinous exudate. Later this bubble may be absorbed and replaced by fresh serous exudate which has little resemblance to that in surrounding alveoli. In two instances Wolbach has seen an identical layer of hyaline fibrin surrounding bubbles of air drawn with interstitial emphysema into the areolar tissue of the mediastinum, the site of mediastinitis caused by the pneumococcus.

Hyaline thrombosis of capillaries within the alveolar walls has repeatedly been described. (Le Count, Lucke, Wight and Kime and others) and has been found associated with the formation of a hyaline lining of dilated alveolar ducts (Brannan and Goodpasture).

Unresolved or Organizing Bronchopneumonia.—This type of bronchopneumonia has been found by all of those who have made autopsies on persons dying two weeks or more after the onset of the symptoms of pneumonia. The lesion was designated productive pneumonia by Delafield (quoted by Symmers). Mac Callum found it as a sequel of measles in February, 1918, at Fort Sam Houston, Texas. He thought it was recognizable before new formation of fibrous tissue occurred, but apparently this has not been the opinion of others. He attributed the lesion to the hemolytic streptococcus, which in his earlier cases was almost invariably cultivated from the lungs. The studies of Cole and Mac Callum showed that streptococcic infection had spread as an epidemic within the hospital at this place and had secondarily infected many patients with pneumonia. The suppurative lymphangitis which is characteristic of infection with the hemolytic streptococcus occurred in some instances (figs. 9 and 10 of Mac Callum). Later following the influenza epidemic at Camp Dix in New Jersey, Mac Callum found an almost identical "interstitial" bronchopneumonia which he believed was caused by the bacillus of Pfeiffer. There were some differences; lymphatic channels in the bronchial walls and widened interlobular septums were inconspicuous, there was no empyema, and polymorphonuclear leukocytes in alveoli and in walls of bronchi were less numerous. It is probable that secondary infection with the hemolytic streptococcus following bronchitis and bronchopneumonia was more frequent at Fort Sam Houston than at Camp Dix.

Bacteriologic studies made by Opie, Blake, Small and Rivers at Camp Pike furnish evidence that the hemolytic streptococcus does not occur more frequently with bronchopneumonia that pursues a chronic course and is accompanied by proliferation of fibrous tissue than with other forms of pneumonia. In bacteriologic examination of seventeen instances of unresolved bronchopneumonia, hemolytic streptococci were found in the bronchi in 30 per cent, in the lungs in 56.2 per cent and in the blood in 55.6 per cent. These figures exceed very little the average incidence of secondary infection with this micro-organism in all forms of postinfluenzal pneumonia, notwithstanding the prolonged course of the disease with unresolved bronchopneumonia. *B. influenzae* of Pfeiffer was not found more frequently with unresolved bronchopneumonia than with other postinfluenzal pneumonia, namely, in bronchi in 80 per cent, in lungs in 68.7 per cent and in the blood in no instance. The bacteriology of bronchopneumonia following influenza has been the subject of much controversy, which has been largely concerned with the part taken by

Pfeiffer's bacillus. It is evident that the agent that causes influenza prepares the way for bacterial invasion of the lower respiratory passages. Goodpasture and Burnett suggest that the primary injury to the lung tissue is due to a potent toxic agent elaborated in and disseminated by the bronchial passages. The character of the acute lesions and the scant number of accompanying bacteria caused these authors to form this opinion, even though they often found Pfeiffer's bacillus in pure culture.

A special method for the demonstration of *B. influenzae* of Pfeiffer in tissues was described by Goodpasture and Burnett. They found the micro-organism in greatest abundance in small bronchi and in adjacent alveoli. Mac Callum, who used a modification of their stain, found Pfeiffer's bacillus in the bronchi, sometimes in clumps and free, but usually enclosed within phagocytic cells. In alveolar exudate, on the contrary, the bacillus was seldom found. Klotz, however, claims to have found small bacilli resembling *B. influenzae* within alveoli in the "early stage" of bronchopneumonia, and Muir and Wilson state that the micro-organism may be found not only in the bronchioles, but in the air vesicles beyond.

The bacillus of Pfeiffer was recovered from the lungs by Keegan in 82.6 per cent of twenty-three autopsies, and from one third of them it was obtained in pure culture. Tytler, Janes and Dobbin, who by preference made cultures from purulent material squeezed from small bronchi, cultivated the same micro-organism from 88 per cent of the lungs from sixty-seven autopsies, but found it, though not infrequently predominant, mixed with a considerable variety of bacteria. Greig has made the noteworthy observation that Pfeiffer's bacillus was recoverable from the bronchial lymph nodes in thirteen of forty-three autopsies on persons who had died of pneumonia following influenza; in twenty-two of fifty examinations, the micro-organism was obtained by culture from the bronchioles, but was not found in the bile or in the kidneys.

Cultures from the consolidated lung tissue have revealed a great variety of bacteria. In the examination (Opie, Blake, Small and Rivers) of forty-seven cases of bronchopneumonia, unaccompanied by lobar pneumonia or by suppuration, pneumococci were found in 42.6 per cent, hemolytic streptococci in 29.8 per cent, staphylococci in 27.7 per cent and *B. influenzae* in 48.9 per cent; *Streptococcus viridans* and *B. coli* were also recovered, but no attempt was made to identify all the micro-organisms in the cultures. The bacillus of Pfeiffer, which was found much more frequently in bronchi (75.7 per cent) than in lung tissue, was in no instance the only micro-organism obtained. Pneumococci and hemolytic streptococci doubtless had an important part in producing the changes that preceded death, for pneumococci had entered the blood of the heart in 31.4 per cent and hemolytic streptococci in 34.3 per cent, and the two infections often coexisted. In some instances, the pneumo-

coccus was recovered from the sputum early in the course of pneumonia and the hemolytic streptococcus later. In hospital wards in which infection with the hemolytic streptococcus was almost wholly absent, pneumonia was invariably caused by the pneumococcus, but in wards in which the patients were heavily infected with the hemolytic streptococcus, both pneumococci and streptococci were obtained from the lungs of those who died. This evidence shows that when bronchopneumonia is caused by the pneumococcus, a superimposed infection with hemolytic streptococcus often occurs. The susceptibility of patients with influenza to reinfection was further shown by recurrent pneumonia in those who had recovered from the earlier disease. The first attack was caused by one type of pneumococcus (type IV) and the second by a different type of pneumococcus (type II) acquired from patients in adjacent beds.

Both in bronchopneumonia and in lobar pneumonia following influenza the predominant types of pneumococci differ from those recovered from cases of lobar pneumonia not associated with influenza. The pneumococci of influenzal pneumonia are those usually present in the mouth, namely, type IV and an atypical variety of II (Medalia, Opie, Freeman, Blake, Small and Rivers, Lamb, Lucke, Wight and Kime) and not the so-called fixed types I and II which in most instances are the cause of lobar pneumonia in the absence of influenza.

Influenza, of which the etiology is not yet determined (*B. pneumosintes,* a filterable virus, and *B. influenzae* of Pfeiffer have received most attention in this relation) causes such injury to the respiratory tract and its accessory structures that they become susceptible to invasion by a variety of bacteria which are constant or transient inhabitants of the upper respiratory passages. When death has occurred as the result of pneumonia, the bacillus or group of bacilli usually designated *B. influenzae* of Pfeiffer is present in abundance together with many other bacteria in the inflamed bronchi, but not all of those who have studied this subject are convinced that the bacillus of Pfeiffer alone causes pneumonia. The pneumonococcus, though by no means the only micro-organism concerned, is predominant in the production of bronchopneumonia. Secondary invasion by hemolytic streptococci occurs frequently and causes changes which will be discussed later.

LOBAR PNEUMONIA

Lobar pneumonia in association with influenza is readily recognizable by its anatomic characters, namely, firm consolidation of lobes or large parts of lobes, coarse granulation of the cut surface, fibrinous plugs within bronchi and uniformly distributed exudate containing abundant fibrin within alveoli. When the consolidation of bronchopneumonia is lobular in distribution, involvement of adjacent secondary lobules causes almost uniform consolidation of wide areas (designated by some writers

confluent lobular or pseudolobar pneumonia), but limitation of the lesion by lobule boundaries is evident (plates xiii and xxvii of Winternitz, Wason and McNamara). The difficulty of differentiating lobar pneumonia and bronchopneumonia following influenza is increased by the frequent association of the two lesions in the same lung, doubtless explained by the severity of changes in the bronchi after influenza.

The recognition of lobar pneumonia comparable to that which occurs in the absence of influenza is confirmed by bacteriologic studies of the United States Army Commission at Camp Pike. In cases regarded as bronchopneumonia, pneumococci were recovered from the bronchi in 48.6 per cent, from the lungs in 42.6 per cent and from the blood in 31.4 per cent, whereas from lungs with lobar pneumonia recognized by its anatomic characters pneumococci were recovered from the bronchi in 66.6 per cent, from the lungs in 82.5 per cent and from the blood in 66.7 per cent.

SUPPURATIVE PNEUMONIA CAUSED BY THE HEMOLYTIC STREPTOCOCCUS

The occurrence of streptococcus pneumonia as a complication of influenza was recognized by Finkler in the great epidemic of 1889-1890, but during two years preceding this epidemic, he saw pneumonia which was presumably primary, but which had a close similarity to the pneumonia of influenza. The disease, he believed, was contagious and in some instances arose in hospital wards. In the spring preceding the pandemic that occurred in September and November of 1918, streptococcus pneumonia was repeatedly seen. Cummings, Spruit and Lynch described pneumonia caused by the hemolytic streptococcus occurring at Fort Sam Houston as a complication of measles or in association with lobar pneumonia, and in a publication that appeared almost simultaneously, Cole and Mac Callum described studies made at the same place. Cole found that patients with lobar pneumonia were infected with hemolytic streptococci in the hospital; patients with measles who entered the hospital without hemolytic streptococci in the throat, later acquired the infection. Streptococcus pneumonia, he says, occurs under conditions which recall the development of puerperal fever and infection of surgical wounds in hospital wards. Miller and Lusk have described an epidemic of streptococcus pneumonia and empyema that occurred at Camp Dodge from March 20 to May 10 of 1918. In May, Mac Callum performed autopsies on persons who died there of the disease and he found streptococcus pneumonia similar to that which he had seen accompanying measles at Fort Sam Houston. Stone, Phillips and Bliss saw at Camp Funston, Kansas, streptococcus pneumonia and empyema in association with a minor epidemic which was evidently influenza (Opie, Freeman, Blake, Small and Rivers) and which preceded the pandemic by several months.

Postinfluenzal pneumonia in which the hemolytic streptococcus was present, studied by Goodpasture at Chelsea, Mass., was accompanied by empyema in eleven of sixteen instances; the hemolytic streptococcus was obtained in pure culture from the pleural exudate. In four instances, there was conspicuous infection of lymphatics and interlobular septums so that lobules in areas of considerable size were marked out by wide yellow bands (interstitial suppuration). Abscesses were found occasionally, and often there was widespread necrosis of consolidated lung tissue. The lesion described as interstitial bronchopneumonia by Mac Callum was not found.

All of those who have studied in detail the lesions produced by the hemolytic streptococcus have found: (*a*) necrosis of lung tissue sometimes implicating the greater part of an entire lobe and readily recognizable by inspection of the lung (fig. 8 of Opie, Blake, Small and Rivers), (*b*) localized abscess formation and (*c*) penetration of streptococci into lymphatics, with thrombosis of these vessels and edema of adjacent fibrous septums, producing in some instances suppuration within and about dilated lymphatics (interstitial suppuration, dissecting pneumonia).

When lobar pneumonia caused by pneumococci is secondarily invaded by the hemolytic streptococcus, characteristic histologic changes are recognizable (Opie, Blake, Small and Rivers) although suppuration has not occurred. Patches of necrosis occur within the consolidated tissue implicating both exuded cells and alveolar walls, and here cocci in chains are present in immense number though scant in adjacent living tissue. In some instances, interlobular septums are edematous and lymphatics are dilated and contain polymorphonuclear leukocytes and streptococci in abundance. Similar changes occur when there is secondary invasion by hemolytic streptococci with bronchopneumonia unaccompanied by abscess formation. Furthermore, in forty instances among the 241 autopsies performed on persons who had died with pneumonia after influenza, well defined abscesses caused by hemolytic streptococci were found, which were almost invariably situated in contact with the pleura and were accompanied by empyema; suppuration of the interstitial tissue of the lungs was seen in twenty-one instances.

The remarkable lesion in which interlobular septums are the site of suppuration due to the hemolytic streptococcus has attracted little attention in this country, although it has been well known to pathologists elsewhere. Mac Callum found it after measles, and describes it in association with peribronchiolar pneumonia which in many of his cases had pursued a chronic course with new formation of fibrous tissue. But this interlobular suppuration, on the one hand, is usually unaccompanied by peribronchiolar consolidation and new formation of fibrous tissue regarded by Mac Callum as distinctive of his interstitial bronchopneu-

monia (unresolved or organizing bronchopneumonia); on the other hand, as Mac Callum later observed, the same peribronchiolar pneumonia with or without organization often occurs in the absence of infection with the hemolytic streptococcus.

Goodpasture saw four instances in which infection of the lymphatics and interlobular tissue with hemolytic streptococcus produced broad yellow bands which followed veins and bronchi to the hilum of the lung. Interstitial suppurative pneumonia is described by Opie, Blake, Small and Rivers (Opie, Blake, Small and Rivers, figs. 10 and 11). Septums distended by suppurating lymphatic vessels often have a beaded appearance caused by constriction at the site of valves. Consolidation of intervening lung tissue may implicate the greater part of lobes, but it does not have the characteristics of lobar pneumonia, being somewhat flabby, and on section, finely granular and a cloudy red or gray. Suppuration within the septums extends, as Ewing has noted, up to the pleural surface, and empyema is present with few exceptions.

SUPPURATIVE PNEUMONIA CAUSED BY STAPHYLOCOCCI

Instances of multiple pulmonary abscesses caused by *Staphylococcus aureus* following influenza were described by Opie, Freeman, Blake, Small and Rivers. Chickering and Park cite from their clinical experience 153 instances of staphylococcus pneumonia. In typical cases the sputum is purulent and salmon pink, and resembles anchovy sauce or the contents of an "overripe furuncle." Sometimes the sputum is blood stained. It contains staphylococci in great number, and cultures demonstrate the presence of the micro-organism. The disease pursues a rapid course and is usually fatal within ten days. Empyema was infrequent in the cases of these authors but occurred occasionally. In a few instances, staphylococci were present in the circulating blood. The changes in the lungs were studied in fourteen autopsies. The cut surface of the lung is, they say, sometimes deep red like spleen pulp, or there may be bronchopneumonia with wide areas of consolidation. Small abscesses from 1 to 10 mm. in diameter, often conspicuous below the pleura, may be scattered throughout the lungs, but in five instances, regarded by the authors as staphylococcus pneumonia, abscesses were not present.

Abscesses of the lung caused by *Staphylococcus aureus* are distinguishable by their macroscopic characters from those caused by the hemolytic streptococcus (Opie, Blake, Small and Rivers). They are small, sharply defined and grouped about terminal bronchi and occur in one or several isolated clusters. Microscopic examination shows that they have been formed by destruction of bronchial walls and extension of suppuration into adjacent alveolar tissue; clumps of staphylococci are found in their contents. In six patients in whom staphylococcic abscesses were present at autopsy, empyema was not found, though the lesion had come into close contact with the pleura.

EMPYEMA

Empyema is a frequent complication of pneumonia following influenza and is in most instances caused by the hemolytic streptococcus which has penetrated by way of the lymphatics to the pleural surface. When this micro-organism has caused suppuration within the substance of the lung (abscess or interstitial suppuration), empyema is almost always present. When an abscess is formed below the pleura, empyema almost invariably follows (Empyema Commission) and is usually limited to the side on which the abscess occurs (Opie, Blake, Small and Rivers).

The formation of pockets containing pus in places in which the parietal and visceral pleura are glued together by fibrin seems to be peculiar to empyema caused by the hemolytic streptococcus. These pockets are usually oval, and the long diameter varies from 1 to 3 cm. (Stone, Phillips, Bliss and others). Thomas has recorded the fatal result of rupture of an encapsulated empyema within the fissure between the upper and lower lobes, the contents escaping into the pleural cavity.

Acute mediastinitis in association with hemolytic streptococcus pneumonia and empyema has been described by Dunham. The micro-organism doubtless finds its way from the hilum of the lung into the mediastinal tissue and comes into contact with the parietal pericardium, not infrequently causing suppurative pericarditis. By way of the areolar tissue about the esophagus, aorta and other blood vessels, it may reach the subperitoneal tissue, and in a few instances general peritonitis has accompanied empyema and pericarditis.

Following influenzal pneumonia, empyema caused by the pneumococcus is much less frequent than streptococcus empyema, and is usually accompanied by abundant accumulation of fibrin. It occasionally implicates the pericardial cavity.

BRONCHIECTASIS

Bronchiectasis following influenza is mentioned by Wolbach (three cases), Goodpasture and Burnett (four cases) and by Winternitz, Wason and McNamara.

The pathogenesis of bronchiectasis following influenza is described by Opie, Blake, Small and Rivers. The lesion in various stages of development occurred in fifty autopsies. In some cases the duration of illness was only eight days, but with advanced bronchiectasis it was usually two weeks or more. Influenza followed by infection of the bronchi with a variety of micro-organisms, including the bacillus of Pfeiffer, hemolytic streptococci and staphylococci causes profound injury to the bronchial wall. There is destruction of the epithelium and later necrosis penetrating more or less deeply, impairing the strength of the muscular coat and extending in some instances into the surrounding alveolar tissue. Where defects in the bronchial wall have occurred, the

edges separate so that part of the circumference of the bronchiectatic cavity is formed by exposed alveoli. Longitudinally directed rents on the inner surface of the bronchus are often seen occurring at intervals about the circumference of the tubule, thus giving the lumen an irregularly stellate form. Alveoli adjacent to these fissures or defects are filled with dense plugs of fibrin.

At the time when these injuries which render the bronchi distensible occur, there is no new formation of fibrous tissue within the bronchial wall or in the surrounding tissue, and dilatation is evidently not due to the traction of fibrous tissue. New formation of fibrous tissue soon begins within and about the injured bronchus, and fibrin within alveoli exposed by necrosis and consequent tears in the bronchial wall undergoes organization. As this new formation of fibrous tissue progresses, a continuous layer is formed in the wall of the bronchiectatic cavity. Occasionally all trace of bronchial wall and exposed alveoli may be obliterated, so that the cavity is surrounded by a continuous wall of fibrous tissue. Epithelium that has survived proliferates and grows over the surface of the enlarged cavity, penetrating into rents in the wall and covering newly formed fibrous tissue. The proliferating epithelium does not have any superficial columnar layer and resembles squamous epithelium.

Parallel with these changes, when the patient lives long enough, there is widespread organizing pneumonia with new formation of fibrous tissue throughout the substance of the lung, but bronchiectasis precedes fibroid pneumonia and is due to changes that impair the strength of the bronchial walls. The pressure within the bronchial lumen closely approximates atmospheric pressure, whereas in adjacent alveoli there is, especially during inspiration, diminished pressure readily measurable within the pleural cavity. Forced inspiration and occlusion of bronchioles by viscid mucopurulent exudate may aid the dilatation of weakened bronchi. (Stages in the development of acute bronchiectasis are illustrated in the monograph of Opie, Blake, Small and Rivers, figs. 17 to 24.)

The bacterial flora of the bronchi with influenza is varied and abundant, *B. influenzae,* hemolytic streptococci, pneumococci, staphylococci and other micro-organisms being found as frequently as with influenzal pneumonia unaccompanied by bronchiectasis. The significance of the bacillus of Pfeiffer in the production of the lesion cannot be determined by the available evidence, but it is doubtless not the only micro-organism concerned.

INTERSTITIAL EMPHYSEMA

Interstitial emphysema is frequently found in association with the pneumonia of influenza. Interstitial emphysema was found in three of thirty autopsies made by Goodpasture and Burnett, and in one of these there was subcutaneous emphysema extending from the superior

mediastinum into the neck. With necrosis penetrating the walls of bronchi and bronchioles, the alveoli may be ruptured so that air penetrates into the interstitial tissue of the lung (Winternitz, Wason and McNamara). How much the distention of lung tissue that occurs with purulent bronchitis and bronchiolitis assists the rupture of alveoli cannot be determined. Air entering the interstitial tissue of the lungs finds the path of least resistance along the blood vessels to the hilum of the lung, and thence along the great blood vessels and bronchi to the mediastinum, over the pericardium into the anterior mediastinum and upward along the trachea to the subcutaneous tissue of the neck (Wolbach). Subcutaneous emphysema may extend from the scalp to the pelvis and scrotum (Berkeley and Coffen).

CHANGES IN OTHER ORGANS

Widespread changes outside of the respiratory organs are described by Lucke, Wight and Kime, Klotz and others, in persons who have died as the result of pneumonia following influenza. Evidence of general intoxication is furnished by cloudy swelling of internal organs; parenchymatous degeneration of kidney tubules is often conspicuous. Fatty changes are seen on the intima of the aorta. The heart muscle usually shows little evidence of injury (Klotz, Wolbach), but Shore has described fatty degeneration of muscle fibers. The spleen is not much enlarged as a rule. In half of those examined, Lucke and his co-workers found that the liver had undergone focal necrosis, and similar changes were found in the pancreas.

Cyanosis frequently associated with influenzal pneumonia may be so intense that the face, lips and upper part of the chest assume an intense dusky reddish-blue hue (different degrees of cyanosis are illustrated by Abrahams, Hallows and French). Bloomfield and Harrop state that the oxygen-combining capacity of the blood in patients with such cyanosis is normal, and they regard the changes in the skin and mucous membranes as an erythematous rash comparable to that of measles. This opinion apparently is not widely accepted (e.g., Torrey and Grosh).

Multiple petechial hemorrhages into the papillary layer of the dermis seen as small bluish-black spots are described by Lucke, Wight and Kime, and were found by them in 20 per cent of the persons who died from influenza. The same observers frequently saw petechial hemorrhages below serous membranes and elsewhere.

Waxy degeneration of voluntary muscles similar to that which occurs with typhoid fever has been repeatedly seen (Mäc Callum, Wolbach, Champtaloup and Drennan, Winternitz, Wason and McNamara, etc.). In thirty-two autopsies in which voluntary muscles were examined by Klotz, the change was found fourteen times in the abdominal recti, sixteen times with hemorrhage in the muscles on both sides and three times

with rupture of one or both muscles; the same degeneration was found twice in the pectoral and twice in the psoas muscles. Symmers saw hemorrhage into the intercostal muscles. Lucke and his associates found abscess of the rectus muscle in two autopsies and cites six cases in which surgical treatment was given.

Changes in the testes similar to those that occur after other infectious diseases have been described by Mac Callum after both streptococcus and pneumococcus pneumonia that occurred in army camps before the pandemic and by Wolbach after influenzal pneumonia. Spermatogenesis ceases and tubules are reduced to simple structures in which sertoli cells have become conspicuous.

Focal necrosis of the suprarenal cortex with hemorrhage is described by Goodpasture and Burnett. Microscopic hemorrhages into the zona reticulata are described by Harris. Wolbach states that hemorrhages into the cortex are usually due to infection with the hemolytic streptococcus. Massive hemorrhage into the suprarenal is seen occasionally.

BIBLIOGRAPHY

Abrahams, A.; Hallows, N. F.; Eyre, J. W. H., and French, H.: Purulent Bronchitis; Its Influenzal and Pneumococcal Bacteriology; Lancet **2**:377, 1917.

Abrahams, A.; Hallows, N., and French, H.: A Further Investigation into Influenzo-Pneumococcal and Influenzo-Streptococcal Septicaemia, Lancet **1**:1, 1919.

Berkley, H. K., and Coffen, T. H.: Generalized Interstitial Emphysema and Spontaneous Pneumothorax, J. A. M. A. **72**:535 (Feb. 22) 1919.

Blanton, W. B., and Irons, E. E.: A Recent Epidemic of Acute Respiratory Infection at Camp Custer, Michigan, J. A. M. A. **71**:1988 (Dec. 14) 1918.

Bloomfield, A., and Harrop, G. A.: Clinical Observations on Epidemic Influenza, Bull. Johns Hopkins. Hosp. **30**:1, 1919.

Bradbury, S., and Krumbhaar, E. B.: Notes on a Month of Influenza at a Base Hospital in France, M. Rec. **95**:594, 1919.

Brannan, D., and Goodpasture, E. W.: The Pathology of Pneumonia Caused by Bacillus Influenzae During an Interepidemic Period, Arch. Int. Med. **34**:739 (Dec.) 1924.

Brem, W. V.; Bolling, G. E., and Casper, E. J.: Pandemic "Influenza" and Secondary Pneumonia at Camp Fremont, California, J. A. M. A. **71**:2138 (Dec. 28) 1918.

Bunting, C. H.: The Leukocytic Picture in Influenza, Am. J. M. Sc. **162**:1, 1921.

Champtaloup, S. T., and Drennan, A. M.: A Preliminary Report on the Recent "Influenza" Epidemic in Dunedin, New Zealand, M. J. Australia **6**:63, 1919.

Chickering, H. T., and Park, J. H.: Staphylococcus Aureus Pneumonia, J. A. M. A. **72**:617 (March 1) 1919.

Christian, H. A.: Incorrectness of the Diagnosis of Death from Influenza; Presence of Bronchopneumonia in Practically All Persons Severely Ill with Influenza, J. A. M. A. **71**:1565 (Nov. 9) 1918.

Cole, R., and Mac Callum, W. G.: Pneumonia at a Base Hospital, J. A. M. A. **70**:1146 (April 20) 1918.

Cumming, J. G.; Spruit, C. B., and Lynch, C.: The Pneumonias: Streptococcus and Pneumococcus Groups, J. A. M. A. **70**:1066 (April 13) 1918.

Dunham, E. K.: Infection in the Mediastinum in Fulminating Cases of Empyema, Surg. Gynec. Obst. **35**:288, 1922.

Empyema Commission: Cases of Empyema at Camp Lee, Va., J. A. M. A. **71**:443 (Aug. 10) 1918.

Ewing, J.: Pulmonary Lesions of Influenza Pneumonia, and a Method of Museum Preparation, Proc. New York Path. Soc. **19**:15, 1919.

Fletcher, W.: Meningococcus Bronchopneumonia in Influenza, Lancet **1**:104, 1919.

Goodpasture, E. W.: Bronchopneumonia Due to Hemolytic Streptococci Following Influenza, J. A. M. A. **72**:724 (March 8) 1919.

Goodpasture, E. W.: The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158**:863, 1919.

Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177, 1919.

Greig, E. D. W.: Observations on the Pathology and Bacteriology of Influenza, Indian J. M. Research **8**:326, 1920.

Harris, D. T.: Some Observations on the Recent Influenza Epidemic, Lancet **2**:877, 1918.

Influenza Committee of the Advisory Board to the D. G. M. S., France: The Influenza Epidemic in the British Armies in France, Brit. M. J. **2**:505, 1918.

Keegan, J. J.: The Prevailing Pandemic of Influenza, J. A. M. A. **71**:1051 (Sept. 28) 1918.

Klotz, O.: The Pathology of Epidemic Influenza, Publications from the University of Pittsburgh School of Medicine: Studies on Epidemic Influenza, 1919, p. 207.

Lamb, F. H.: Primary and Postinfluenzal Pneumonia, J. A. M. A. **72**:1133 (April 19) 1919.

Le Count, E. R.: The Pathologic Anatomy of Influenzal Bronchopneumonia, J. A. M. A. **72**:650 (March 1) 1919.

Disseminated Necrosis of the Pulmonary Capillaries in Influenzal Pneumonia, J. A. M. A. **72**:1519 (May 24) 1919.

Lucke, B.; Wight, T., and Kime, E.: Pathologic Anatomy and Bacteriology of Influenza, Arch. Int. Med. **24**:154 (Aug.) 1919.

Lyon, M. W.: Gross Pathology of Epidemic Influenza at Walter Reed General Hospital, J. A. M. A. **72**:924 (March 29) 1919.

Mac Callum, W. G.: Pathology of the Epidemic Streptococcus Bronchopneumonia in the Army Camps, J. A. M. A. **71**:704 (Aug. 31) 1918.

A Stain for Influenza Bacilli in Tissues, J. A. M. A. **72**:193 (Jan. 18) 1919.

Pathology of the Pneumonia Following Influenza, J. A. M. A. **72**:720 (March 8) 1919.

Pathology of Epidemic Pneumonia in Camps and Cantonments in 1918, M. Rec. **95(1)**:776, 1919, and Tr. Assn. Am. Phys. **34**:169, 1919.

The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-18, New York, Rockefeller Institute, Monograph no. 10, 1919.

Pathological Anatomy of Pneumonia Associated with Influenza, Johns Hopkins Hosp. Rep. **20**:149, 1921.

Medalia, L. S.: Influenza Epidemic at Camp Mac Arthur: Etiology, Bacteriology, Pathology and Specific Therapy, Boston M. & S. J. **180**:323, 1919.

Meleney, H. E., and Pappenheimer, A. M.: Pathological Findings in Seventeen Cases of Pneumonia During the Influenza Epidemic of January-February, 1920, Proc. New York Path. Soc. **20**:56, 1920.

Miller, J. L., and Lusk, F. B.: Epidemic of Streptococcus Pneumonia and Empyema at Camp Dodge, Iowa, J. A. M. A. **71**:702 (Aug. 31) 1918.

Muir, R., and Wilson, G. H.: Influenza and its Complications, Brit. M. J. **1**:3, 1919.

Nuzum, J. W.; Pilot, I.; Stangl, F. H., and Bonar, B. E.: Pandemic Influenza and Pneumonia in a Large Civil Hospital, J. A. M. A. **71**:1562 (Nov. 9) 1918.

Opie, E. L.; Freeman, A. W.; Blake, F. S.; Small, J. C., and Rivers, T. M.: Pneumonia at Camp Funston, J. A. M. A. **72**:108 (Jan. 11) 1919.

Pneumonia Following Influenza (at Camp Pike, Ark.), J. A. M. A. **72**:556 (Feb. 22) 1919.

Opie, E. L.; Blake, F. S.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease; the Pneumonias and Other Infections of the Respiratory Tract Accompanying Influenza and Measles, St. Louis, 1921.

Patterson, J. W.; Little, E. M., and Williams, S. E.: Report on the Bacteriology and Pathology of Forty-Six Fatal Cases of Influenza, Nat. Health Insurance, M. Research Com., London, 1919, no. 36, p. 88.

Shore, T. H. G.: Report on the Morbid Anatomy of Influenza, Nat. Health Insurance, M. Research Com., London, 1919, no. 36, p. 96.

Stone, W. J.; Phillips, B. G., and Bliss, W. P.: A Clinical Study of Pneumonia Based on Eight Hundred and Seventy-One Cases, Arch. Int. Med. **22**:409 (Oct.) 1918.

Stone, W. J., and Swift, G. W.: Influenza and Influenzal Pneumonia at Fort Riley, Kansas, J. A. M. A. **72**:487 (Feb. 15) 1919.

Sundell, C. E.: The Morbid Anatomy of Influenza, Nat. Health Insurance, M. Research Com., London, 1919, no. 36, p. 65.

Symmers, D.: A Note on the Pathology of the Prevailing Pandemic Influenza, New York M. J. **108**:621, 1918.

Pathologic Similarity Between Pneumonia of Bubonic Plague and of Pandemic Influenza, J. A. M. A. **71**:1482 (Nov. 2) 1918.

Symmers, D., Dinnerstein, M., and Frost, A. D.: Differences in Pathology of Pandemic and Recurrent Forms of So-Called Influenza, J. A. M. A. **74**:646 (March 6) 1920.

Thomas, H. M., Jr.: Rupture of Encapsulated Empyema into the Pleural Cavity, J. A. M. A. **72**:29 (Jan. 4) 1919.

Torrey, R. G., and Grosh, L. C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia, Am. J. M. Sc. **157**:170, 1919.

Tytler, W. H.; Janes, R. M., and Dobbin, G. M.: Pathological and Bacteriological Findings in Fatal Cases of Pneumonia During the Influenza Epidemic of October and November, 1918, Nat. Health Insurance, M. Research Com., London, 1919, no. 36, p. 77.

Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, New Haven, Yale University Press, 1920.

Wolbach, S. B.: Comments on the Pathology and Bacteriology of Fatal Influenza Cases as Observed at Camp Devens, Mass., Bull. Johns Hopkins Hosp. **30**:104, 1919.

Notes and News

University News, Promotions, Resignations and Appointments.—A portrait of William F. Whitney, curator of the Warren Museum of the Harvard Medical School from 1879 to 1921 and pioneer clinical pathologist, was unveiled in the Warren Museum, Nov. 18, 1927.

Francis D. Gunn, assistant in pathology at the University of Buffalo and fellow in pathology of the National Research Council, has been appointed pathologist to Wesley Memorial Hospital, Chicago.

Frederick H. Dieterich has been made director of the bureau of laboratories, department of public health, Yonkers.

At the New York Homeopathic Medical College, Lindsley F. Cocheu has been placed in charge of bacteriology and clinical pathology, Laura Florence has been made assistant professor of bacteriology and William H. Probert has been made assistant professor of pathology.

R. J. Hibbard and Stewart Wallace, of the department of pathology, Tulane University, have been appointed professor of pathology and director of laboratories, respectively, in Baylor University, Dallas, Texas.

William G. MacCallum, professor of pathology and bacteriology in the Johns Hopkins University, was given the honorary degree of doctor of science on the occasion of the centenary celebration of the University of Toronto.

At the University of Missouri, Dudley A. Robnett has been promoted to assistant professor of pathology.

Montrose T. Burrows has resigned as associate professor of experimental surgery in Washington University, St. Louis, and as director of the research laboratory of the Barnard Free Skin and Cancer Hospital, and will go into the practice of surgery in Pasadena, Calif.

Domoso Rivas, assistant professor of parasitology in the University of Pennsylvania, has taken up the directorship of pathology in the Pan American Hospital in New York, dedicated on Oct. 16, 1927.

Roy S. Leadingham has been appointed pathologist to the Grady Hospital (White Unit), Atlanta, Ga.

At the University of Michigan, Philip Hadley has been promoted to associate professor of bacteriology.

Stephen Gaspard has been placed in charge of the laboratories of the City Hospital, Rochester, N. Y.

Sidney Dalrymple has been appointed assistant in pathology in the Boston University School of Medicine.

Ethel Barrow and George L. Kilgore have been appointed fellows in pathology, and George F. C. Fasting, fellow in bacteriology, in the Mayo Foundation, Rochester, Minn.

At the Long Island College Hospital, Archibald Murray has retired from the professorship of pathology, and Wade W. Oliver, professor of bacteriology, has been placed in temporary charge of the department. Max Lederer has been appointed associate professor of pathology.

The University of Chicago has conferred the honorary degree of doctor of science on Karl Landsteiner of the Rockefeller Institute for Medical Research.

Fund for Study of Infantile Paralysis.—Announcement is made that $5,000 annually has been given to the University of California to promote investigation of infantile paralysis or other diseases of children.

French Medicolegal Congress.—At a meeting of the Congrès de médecine légale de langue française, in Lyon in July, 1927, it was decided to enlarge

the name of the society to include "Médecine sociale, accidents du travail et maladies professionelles." The next meeting will be held in Paris in October, 1928, with the Congress of Surgery, and with Georges Brouardel as president.

The U. S. Government Wants Pathologists.—The U. S. Civil Service Commission, Washington, D. C., announces that examinations will be held for the position of associate pathologist to fill various vacancies. The entrance salaries are from $2,400 to $3,000 with opportunities for advancement.

Pasteur Institute in Montreal.—It is reported that Professor A. Pettit of the Institut Pasteur, Paris, has been appointed by the French government to organize a Pasteur institute at Montreal at the request of the University of Montreal, of which it will be a department.

Celebration in Honor of Adolpho Lutz.—The seventieth birthday of Dr. Adolpho Lutz, as the pioneer of biology, parasitology and experimental medicine in Brazil, has recently been celebrated in that country. He was born of Swiss parents at Rio de Janeiro. After receiving his medical degree at the University of Berne, he spent some time in the medical centers of Europe, and studied leprosy at Honolulu. In 1892, he took charge of the bacteriologic institute at S. Paulo, Brazil, and his indefatigable research threw much light on malaria, hookworm and yellow fever and the intermediate hosts in various diseases. His studies of mosquitoes, tenias, scorpions, snakes, snails, etc., revealed numerous new species, and the transmission of *Schistosomum mansoni* by fresh water snails. Dr. Carlos Chagas says of him in the last "Memorias do Instituto Oswaldo Cruz," with which Lutz has been connected since its foundation, that his scientific work is the most notable that has ever been realized by a single worker in the history of Brazil. He is still actively and fruitfully engaged there.

Syphilitic Infection from Cadaver.—Hoffmann (*Deutsche med. Wchnschr.* **53**:1501, 1927) emphasizes that it has been shown by experience and by experiment that syphilis may be acquired from the human cadaver. He found twenty certain, fourteen probable and four merely mentioned cases in the literature. In the twenty certain cases the chancre was nearly always on the finger (three on the index finger, four on the thumb, ten on other fingers). Once the primary lesion was on the neck. The course of the disease was usually severe. In three cases, there was malignant syphilis; in one case, early syphilis of the brain. Many of the infections were tardy. Infection is easiest from cadavers of congenitally syphilitic children and fetuses; rarer from those of adults with early syphilis; exceptional in paralysis. The infrequency of infection from cadavers is due, apparently, to the early weakening of the virus, while the penetrative faculty of *Spirocheta pallida*, important for the ordinary infection, is reduced because of injury to its terminal filament and cortical substance. The greatest cleanliness and care are advisable in making necropsies.

Abstracts from Current Literature

Pathologic Physiology

STUDIES IN EXPERIMENTAL EXHAUSTION DUE TO LACK OF SLEEP: III. EFFECT ON THE NERVE CELLS OF THE SPINAL CORD. T. H. BAST, F. SCHACHT and H. VANDERKAMP, Am. J. Physiol. **82**:131, 1927.

This paper is one of a series published in this issue of the *American Journal of Physiology*. In the first two the method used to induce exhaustion and the symptomatology of this type of exhaustion in the rabbit are described. In cases of extreme exhaustion induced by loss of sleep, the following changes were noted in the nerve cells of the spinal cord: (1) decrease in nuclear chromatin content; (2) chromatolysis, characterized by granulation of the Nissl bodies or diffusely throughout the cytoplasm, and vacuolization of the cytoplasm. This vacuolization usually occurred in a zone midway between the wall of the cell and the nucleus.

H. E. EGGERS.

STUDIES IN EXPERIMENTAL EXHAUSTION DUE TO LOSS OF SLEEP: IV. EFFECTS ON THE NERVE CELLS OF THE MEDULLA. T. H. BAST and W. B. BLOEMENDAL, Am. J. Physiol. **82**:140, 1927.

Following exhaustion to the point of collapse in rabbits from loss of sleep, in the nerve cells of the medulla, chromatolysis was observed in the cells of the reticular formation, commissural nucleus of the solitarius and in the dorsal nucleus of the vagus. This was characterized by granulation of the Nissl bodies, vacuolization of the cytoplasm, either midway between the wall of the cell and the nucleus or at the periphery of the cytoplasm, and partial loss of nuclear staining power. The portion of the nucleus retaining this power is clustered around and radiates from the nucleolus, which is not affected. Nuclear migration was not observed.

Changes were not observed in the cells of the hypoglossal nucleus or in any motor nerve cells supplying somatic musculature.

It may be well to comment that there was a certain amount of muscle fatigue in the experimental conditions.

H. E. EGGERS.

EXPERIMENTAL HYPERTHYROIDISM. M. M. KUNDE, Am. J. Physiol. **82**:195, 1927.

In hyperthyroidism induced in either normal or thyroidectomized dogs and rabbits by the administration of thyroxin or desiccated thyroid, in either single or repeated doses, the following results were noted:

With a single dose, a change was not observed in the metabolic rate for from seven to twelve hours; then a definite rise occurred, which was most marked on the second day. Repeated administration caused a progressive increase in the metabolic rate, reaching its maximum three weeks or more after the initiation of the experiment. The maximal rise in normal dogs was 120 per cent above normal; in previously thyroidectomized dogs, 170 per cent. There always was accompanying fever. Tachycardia and disturbed conductive mechanism of the heart were observed at times.

The effect on weight was dependent on an undetermined nutritional state; some dogs retained constant weight during several weeks of advanced hyperthyroidism on maintenance diet; others lost 35 per cent of their initial weight.

Diarrhea, tenesmus and bloody stools occasionally resulted, and in some dogs severe eczematous lesions of the skin appeared during the crisis of the intoxication. Hyperglycemia and glycosuria were not observed. Exophthalmos was not demonstrable in the dogs on which experiments were made, but in

previously thyroidectomized rabbits it appeared to a pronounced degree when thyroid material was administered to excess.

Pronounced degenerative changes were observed in the thyroids of the intoxicated animals. There was a generalized disintegration of the gland, with flattening of the follicular lining epithelium to an extreme degree.

The administration of iodine, as either potassium iodide or free iodine, did not have any effect on the metabolic rate of normal or intoxicated dogs.

From the foregoing observations, the author concludes that there is no evidence of the activity of a perverted secretion in the production of the outstanding clinical symptoms of hyperthyroidism. She does not find any evidence of a quantitative relationship between the amount of thyroid substance administered and the increase in basal metabolism, nor can her results be explained by the catalytic theory of Plummer and Boothby; she believes that the intoxication is related to water metabolism and dehydration. Thyroidectomy made the animals more susceptible to intoxication. H. E. Eggers.

Traumatic Cyanosis — Its Pathological Physiology. M. S. Rosenblatt, Ann. Surg. **85**:801, 1927.

Traumatic cyanosis is a phenomenon produced by the suspension of respiration for a time due to forced compression of the thorax or thorax and abdomen. A report of a case is given, and the theory that the distribution of the cyanosis is due to the incompetent or absent valves in the large veins of the upper part of the thorax and neck is supported. This incompetency allows the pressure in the superior vena cava to cause distention and stasis in the small peripheral veins. N. Enzer.

Fragilitas Ossium. Its Hereditary Aspect with Case Report. M. S. Rosenblatt, J. Michigan M. Soc. **26**:292, 1927.

The patient, an American girl, aged 12, had a fracture of the femur and had previously had fifteen fractures of the long bones. From her maternal great-grandfather had descended nine sons and (from one son) eight grandchildren (four boys, four girls) all of whom had multiple fractures. From the histories, apparently only one of these (a grandchild, the mother of the patient) had blue sclerae. The expectation that only 50 per cent of the offspring of an affected person married to an unaffected person will be affected did not hold true in this family, and neither did the rule (Key) that in such families the offspring with normal sclerae will have normal children. Attention is called to the differentiation of osteopsathyrosis idiopathica, osteogenesis imperfecta and hereditary hypoplasia of the mesenchyme which are mentioned as synonyms by Osler.

Experimental Stone in the Bladder. R. McCarrison, Indian J. M. Research **15**:197, 1927.

A diet of whole wheat flour, linseed meal, corn flour, salt and calcium phosphate proved to be potent in causing the formation of stones in the bladder in rats. This diet approaches in quality that used by the people in stone-areas in Northern India.

Experimental Goiter Unrelated to Iodine. R. McCarrison, Indian J. M. Research **15**:247, 1927.

In young rats a diet containing more than 60 per cent white flour or vitamin-poor carbohydrate, 20 per cent or less of protein with fats and inorganic salts including iodine, in adequate amounts, but not containing green vegetables or fruits, produced a definite goiter. An intense secretory hypertrophy of the thyroid was followed by replacement of secretory cells with fibrous tissue.

THE HORMONE OF THE ANTERIOR HYPOPHYSEAL LOBE. I. DEMONSTRATION OF ITS PRESENCE. B. ZONDEK and S. ASCHHEIM, Klin. Wchnschr. **6**:248, 1927.

The administration of the hormone of the anterior lobe of the pituitary gland causes an infantile mouse to go into heat, but does not affect a castrated animal. The hormone acts by starting ripening of the ovarian follicles and mobilizing the ovarian hormone. This then specifically affects the uterus and vagina and causes heat. The pituitary hormone is the primary sex hormone, but works only by way of the ovarian or secondary sex hormone.

J. D. WILLEMS.

Pathologic Anatomy

MALIGNANT NEUROBLASTOMA. B. KWARTIN and J. R. TWISS, Am. J. Dis. Child. **34**:61, 1927.

Three cases of abdominal neuroblastoma are reported in children aged from 3 months to 3½ years. Each patient presented an enlarged abdomen, cachectic anemia and multiple metastases.

RUTH E. TAYLOR.

SICKLE CELL ANEMIA. W. B. STEWART, Am. J. Dis. Child. **34**:72, 1927.

A review of the literature is given and a case reported in a child of Cuban descent. The child had been under observation for five and one-half years, and during this time the spleen passed from a greatly enlarged to an atrophic condition.

RUTH E. TAYLOR.

ADENOMA OF SALIVARY GLANDS. JOSEPH MCFARLAND, Am. J. M. Sc. **174**:362, 1927.

An adenoma of the parotid is reported. After thorough consideration, it is placed "at one end of a long series of tumors, at the other extreme of which are the ordinary mixed tumors."

MYOSITIS OSSIFICANS PROGRESSIVA. AMOS R. KOONTZ, Am. J. M. Sc. **174**:406, 1927.

One hundred and thirty-four cases have been reported of this strange disease, which is marked by multiple, if not by general, ossification of the voluntary muscles of the body, without apparent cause. In most cases there is also a congenital anomaly of the great toes or thumbs (micro-dactylia or brachy-dactylia). Koontz describes the one hundred and thirty-fourth case and reviews the literature briefly.

THE RELATION BETWEEN CHOLESTEROLEMIA AND DEPOSITS OF CHOLESTEROL IN THE GALLBLADDER: AN EXPERIMENTAL STUDY. F. E. BLAISDELL and L. R. CHANDLER, Am. J. M. Sc. **174**:492, 1927.

A hypercholesterolemia was produced in all animals by feeding cholesterol. A continued hypercholesterolemia resulted in deposits of cholesterol containing fat in certain characteristic cells in the mucosa and submucosa of the gallbladder, when the cystic duct was patent. This occurred in both rabbits and dogs, but more readily in the latter. When the cystic duct was ligated before feeding cholesterol, the hypercholesterolemia was produced, but cholesterol-containing fat was not found in the wall of the gallbladder, not even in the epithelium. The deposits of cholesterol in the wall of the gallbladder are dependent on absorption of cholesterol from the bile.

AUTHORS' SUMMARY.

CIRCULATORY FACTORS INFLUENCING FORMAL OSTEOGENESIS. J. J. MORTON and S. J. STABINS, Ann. Surg. **86**:430, 1927.

Retardation of healing at the site of a fracture and retardation of regeneration of the bone resulted from blocking the venous drainage by tying the saphenous vein. The experiments were performed on white rats and dogs.

N. ENZER.

PRIMARY ULCER OF THE JEJUNUM. I. S. RAVDIN, Ann. Surg. **85**:873, 1927.

A case of primary ulcer of the jejunum is reported, and brief remarks on previously reported cases are given.

N. ENZER.

THE ARTERIOLAR LESIONS OF GLOMERULONEPHRITIS. ARTHUR M. FISHBERG, Arch. Int. Med. **40**:80, 1927.

The arteriolar lesions of diffuse glomerulonephritis are of four histologically and pathogenetically distinct varieties:

1. Acute necrotizing arteritis was found in the renal arterioles in three of eight patients dying during the acute stage of diffuse glomerulonephritis. These lesions are probably of the same (toxic?) origin as the glomerular lesions.

2. Endarteritis obliterans was present in seventeen of twenty-nine cases of chronic diffuse glomerulonephritis in various stages. Endarteritis obliterans was not found in the early stages or often in the end-stage (scondary contracted kidney); it occurred predominantly in those patients who succumbed after the process in the glomeruli was still active. The histology of the lesion is identical with that seen when an artery is ligated, and the opinion is advanced that the endarteritis obliterans is due to the glomerular lesion blocking the blood current.

3. Arteriolosclerosis similar in histology and distribution of the lesions to that found in essential hypertension was present in all twelve cases of secondary contracted kidney. It was not found in early cases and was of but slight degree in the moderately advanced cases. The occurrence of arteriolosclerosis is correlated with hypertension of long duration.

4. Muscular hypertrophy in the media of the renal arterioles was well marked in many cases of chronic glomerulonephritis of considerable duration but still "active." It was not found in the early stages. In cases of secondary contracted kidney of many years' duration the medial muscle usually atrophies as it does in essential hypertension.

AUTHOR'S SUMMARY.

MULTIPLE MYELOMA WITH REPORT OF A CASE. THOMAS J. CHARLTON, Arch. Int. Med. **40**:98, 1927.

A case report of multiple myeloma occurring in a woman, the patient being under observation for over two and one-half years, is given. Attention was first directed to the condition by a pain in the back, made worse by pressure. Bence-Jones protein was found in the urine, and on the basis of these two conditions a provisional diagnosis of multiple myeloma was made; roentgen-ray observations confirmed the diagnosis. The blood picture was that of marked secondary anemia. The icteric index and hemosiderosis of the liver and spleen at autopsy suggested that the anemia to a certain extent may have been of a hemolytic nature. The course of the disease was marked by progressive anemia and many pathologic fractures. At autopsy several pathologic fractures were seen, and most of the bones were destroyed by the tumor growth of the marrow. The histologic structure of the tumor tissue was that of a plasmocytoma. Metastases were not found, but plasma cells were present in the capillaries of the liver.

AUTHOR'S SUMMARY.

YELLOW ATROPHY OF THE LIVER. ACUTE, SUBACUTE AND HEALED. J. D. WILSON and E. W. GOODPASTURE, Arch. Int. Med. **40**:377, 1927.

Cases illustrative of an acute, a subacute and a healed yellow atrophy of the liver are presented. Recovery from acute yellow atrophy is probably more frequent than is generally believed. Different stages of the disease have been accurately recognized pathologically, namely, acute, subacute, chronic and healed stages. In the healed stage, the liver is grossly and irregularly lobulated. The hepatic parenchyma is represented by irregular masses of hyperplastic liver cells, which are separated by a vascular, collapsed stroma in which the skeleton of previous lobules persist to a greater or less degree. From this histologic picture the diagnosis may be made. As the initial lesion of acute yellow atrophy differs in distribution and in extent, if not in kind, from that of the ordinary toxic central necrosis, and as we are yet ignorant of the etiology, it is believed that the term "healed yellow atrophy of the liver" is preferable to the term "toxic cirrhosis" as applied to the condition of the liver which is healed.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF CHRONIC SUBDURAL HEMATOMA AND PACHYMENINGITIS HEMORRHAGIA INTERNA. R. A. GRISWOLD and F. JELSMA, Arch. Surg. **15**:45, 1927.

Necropsy results in eight cases are presented. The hemorrhage nearly always followed slight trauma. The reaction of the dura to the blood clot takes the form of proliferation of the endothelial cell, and the authors believe that the characteristic spaces lined by endothelium result from proliferation of detached bits of dural endothelium in the clot. These communicate with blood spaces and may give rise to secondary hemorrhages by rupture following slight increases in intracranial tension. A history of trauma was not given in all of the cases, but the histologic appearances were the same in all. Some of the clots showed a high concentration of bilirubin. The green pigment in these cases has been commented on by Cushing. The cells of the leptomeninges take up red blood cells and give rise to bilirubin. There was a history of alcoholism in five cases. Alcoholism is an important factor in the causation. Trauma was usually slight, and a predisposing vascular lesion seems likely.

N. ENZER.

RELATION OF THE PYLORUS TO DURATION OF EXPERIMENTAL GASTRIC ULCER. W. HUGHSON, Arch. Surg. **15**:66, 1927.

Ulcerative defects in the lesser curvature of the stomach of dogs were produced by excision of small pieces of mucosa and infiltration with silver nitrate. In one half of the dogs operated on, a splinting of the pyloric opening was performed rendering it permanently patent. In such dogs, the ulcers healed more rapidly than in those in which the pylorus was not splinted. This splinting overcomes the delay in emptying time which results from spasm of the pylorus by irritation from the ulcer. Experimental ulcers cause a delay in the emptying time; by obviating this, healing is promoted.

N. ENZER.

DEPOSITION OF CALCIUM SALTS IN AREAS OF CALCIFICATION. J. C. WATT, Arch. Surg. **15**:89, 1927.

As a result of his studies on calcification as it occurs in the pineal gland, various arteries, the choroid plexus and the thyroid, Watt believes the process of calcification is one of precipitation of calcium salts from the blood and is not a secretory phenomenon. He demonstrates the position of the calcium in sections and proves the deposit to be calcium by various staining reactions, solubility in acids and their close structural resemblance to the deposits of calcium salts when precipitated in colloidal solutions.

N. ENZER.

EXPERIMENTAL OBSERVATIONS ON THE GROWTH OF LONG BONES. GATEWOOD and B. P. MULLEN, Arch. Surg. **15**:215, 1927.

Lead shot was introduced at carefully measured intervals into the femur of young rabbits. As measured by the roentgen ray, no growth occurs in the shafts. This proved to be so under normal conditions as well as when an increased functional demand was created by artificial closure of the epiphyses. This was done by destroying the cartilage nearest the joint.

N. ENZER.

FATAL PULMONARY EMBOLISM. E. F. HENDERSON, Arch. Surg. **15**:231, 1927.

In 6 per cent of the necropsies, it was found that death was the result of pulmonary embolism resulting from surgical procedures. The studies of these cases show that the average age and weight of the patients are higher than in the average patients on whom operation is performed and that the blood pressure is slightly lower. Postoperative infection was present in a large percentage.

N. ENZER.

THE RELATION OF OBESITY TO FATAL POSTOPERATIVE PULMONARY EMBOLISM. A. M. SNELL, Arch. Surg. **15**:237, 1927.

A high incidence of pulmonary embolism was found in obese patients.

N. ENZER.

POSTOPERATIVE PHLEBITIS. G. E. BROWN, Arch. Surg. **15**:245, 1927.

Unless tenderness along the course of the veins was present, a diagnosis of phlebitis was not made. Edema and fever are important corroborative signs, also pulmonary infarctions. Fatal pulmonary embolism did not occur in eighty-seven cases of this condition. Most of the cases occurred in the spring and fall. Bacteriologic studies did not yield positive results.

N. ENZER.

STATUS THYMICO-LYMPHATICUS CONSIDERED IN THE LIGHT OF RECENT WORK ON THE THYMUS. MAJOR GREENWOOD and HILDA M. WOODS, J. Hyg. **26**:305, 1927.

The concept of a status thymicolymphaticus so far as it is scientific belongs at present wholly to the statistical order of ideas and is in pari materia with the concept of racial susceptibility to disease. It is possible, for instance, that Swedish people are more susceptible to pulmonary tuberculosis than English. A practitioner confronted with a case of pulmonary tuberculosis might reasonably take the racial factor into account, and, other things equal, give a more cautious prognosis when the patient is Swedish than when he is English. But if the case had ended fatally much sooner than his general experience of the physical signs and symptoms of phthisis had led him to expect, he would hardly record on the death certificates: phthisis—Swedish nationality. The present use in certification and in evidence in coroners' courts of the phrases status lymphaticus and status thymicolymphaticus is a good example of the growth of medical mythology. A nucleus of truth is buried beneath a pile of intellectual rubbish, conjecture, bad observations and rash generalization. This heap of rubbish is described in the current scientific jargon and treated as an orthodox shrine. Indeed, when men of science speculate as to the nature of the antiepinephrine produced to excess in status thymicolymphaticus, one feels how well merited was the rebuke administered to some clinical endocrinologists by G. N. Stewart, who, in discussing certain papers on "hypoadrenal" constitutions, said: "In reading this paper and many others by 'clinical endocrinologists,' especially the French and the Italians, the physiologist can scarcely escape the feeling that here he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism are becoming foolishness, where fact and hypothesis are

habitually confounded and nothing is but what is not." At the present moment we have not sufficient knowledge of the frequency of the single and combined anomalies which have been thought to define anatomically status lymphaticus or status thymicolymphaticus in a healthy population to permit us to assign the least importance to the recognition of these stigmas in the bodies of those whose deaths, apart from status lymphaticus, would in more pious, but not more superstitious, days have been attributed to the visitation of God.

AUTHORS' SUMMARY.

THE EFFECT OF VENOUS STASIS ON THE PROTEINS OF BLOOD PLASMA AND ON THE RATE OF SEDIMENTATION OF THE RED BLOOD CORPUSCLES. E. D. PLASS and M. D. ROURKE, J. Lab. & Clin. Med. **12**:735, 1927.

Prolonged venous stasis leads to dehydration of blood and to an increase of plasma proteins. The fibrin, globulin and albumin are each increased and to a greater extent than can possibly be accounted for by concentration of the plasma alone. The increase in the separate proteins are not equal to each other, nor is any one consistently higher or lower than the others. Authors believe that certain catabolic products formed in the tissues by reason of the anoxemia imposed by the venous stasis have acted on the cell "membranes" of both the capillaries and the tissue cells, increasing their permeability to protein. It is suggested that the lymph fluid has increased in protein content by diffusion of protein from the cytoplasm of the tissues which it surrounds, and that this lymph fluid, having become higher in protein than normal plasma, subsequently loses protein to the plasma, thereby increasing the total plasma proteins. The marked increase in fibrin during venous stasis points to reserve fibrin in the tissues. The sedimentation rate is increased by prolonged venous stasis, and it is suggested that the increase is probably due chiefly to increased fibrin.

S. A. LEVINSON.

OSTEOCLASTOMA (MYELOID SARCOMA) OF THE HUMAN FEMALE BREAST. H. J. B. FRY, J. Path. & Bact. **30**:529, 1927.

A "teratoid" mixed tumor of the breast is described, in which the predominant feature is the presence of multinucleated giant cells of "myeloid" type. These cells seem to be "foreign-body" giant cells of the nature of osteoclasts. The cartilaginous and osteoid tissue appears to be derived by metaplasia from the fibrous tissue of a fibro-adenoma to which the sarcomatous tissue and giant cells are regarded as a tissue reaction.

AUTHOR'S SUMMARY.

NEOPLASMA OF THE CHEST. J. E. A. LYNHAM, Tubercle **8**:262, 1927.

This is essentially a clinical and roentgenologic study of neoplasms in the chest, considering carcinoma, sarcoma, dermoid cysts, fibroma and other tumor conditions, primary as well as secondary.

H. J. CORPER.

BINUCLEATE CELLS AND GIANT CELLS IN TISSUE CULTURES AND THE SIMILARITY OF THE LATTER TO THE GIANT CELLS OF TUBERCULOUS LESIONS. WARREN H. LEWIS, Tubercle **8**:317, 1927.

The conclusions and material in this article are closely identical to that published in the *Am. Rev. Tuberc.* **15**:616, 1927.

H. J. CORPER.

AN EXPERIMENTAL STUDY ON THE GENESIS OF THE INITIAL STAGES OF CIRRHOSIS OF THE LIVER. JOSEPH F. MARTIN, Ann. de méd. **21**:89, 1927.

Martin tried to induce cirrhosis of the liver in guinea-pigs by using the method of Findlay. The animals received 5 mg. of manganèse de chlorine in 1 cc. of distilled water subcutaneously and were killed at different intervals

following the injection. He arranges the hepatic lesion chronologically as follows: (1) an insular periportal vasodilatation; (2) mitochondriolysis at different stages, preceding the alteration of the cellular cytoplasm; (3) granular, fatty, or atrophic degeneration of cells gathered in rings; (4) a mesenchymatous reaction around the areas of the degenerated parenchyma; (5) destruction of the parenchymatous elements by scar tissue. The value of changes in mitochondria as an indicator of the incipient stages of hepatic cirrhosis is emphasized. The lesion starts in the parenchyma, and is followed later by involvement of the interstitial tissue.

B. M. FRIED.

ABDOMINAL LYMPHOSARCOMA WITH METASTASIS IN THE CRANIOFACIAL BONES; FALSE CHLOROMAS. A. VOLPE and N. L. BLOISE, Arch. d. méd. d. enf. **30**: 73, 1927.

Two cases of primary lymphosarcoma of the perirenal lymph glands in children are reported with exhaustive clinical data and complete postmortem observations. In each case there was extensive metastasis in the flat bones, especially in those of the cranium and of the face affording, in the latter instance, a typical picture of chloroma. In addition, there was an intense anemia, giving a greenish-yellow tinge to the skin; the liver was enlarged and there was hyperplasia of all the accessible lymph nodes. The patients were boys, aged 3 and 4 years, respectively, who had died during the fourth month of invasion. Particular attention is invited to the differential diagnosis in such cases; not only should careful study of the blood be made, but also examination by puncture of the neoplastic pulp, the marrow and the spleen.

CLINICAL AND STATISTIC OBSERVATIONS ON MYOMAS OF THE STOMACH. P. NIGRISOLI, Arch. per le sc. med. **49**:1, 1927.

Nigrisoli describes one case of leiomyoma of the stomach in a woman whose mother died from a malignant abdominal tumor and one of whose sisters was operated on for a benign abdominal tumor and another for an ovarian cyst. He collected seventy other cases in the literature (from 1914 to October, 1926), which he adds to Nassetti's statistics of 140 myomatous tumors of the stomach, collected in 1914. Among these 211 cases, 99 were myomas, 53 fibromyomas, the rest myosarcomas and other tumors of myomatous origin. A detailed survey of the collected cases—including the clinical diagnosis—is added.

K. SCHULHOF.

GRANULOMATOUS FORM OF PRIMARY SPLENOMEGALY (SPLENOGRANULOMA). C. GAMNA, Arch. per le sc. med. **49**:109, 1927.

Gamna deals with the papers of various authors who confirmed—with some exceptions—the existence of a peculiar morbid entity described by him in 1922. He published the report of several cases of primary splenomegaly with little if any changes in the blood. The changes are limited to the spleen and the adjacent lymph nodes. The follicular apparatus of the spleen is intact, while there is a proliferation of granulomatous tissue from the fixed adventitial reticulo-endothelial elements of the pulp. The collagen and elastic fibers and the walls of the blood vessels of the spleen present a hyaline degeneration and impregnation with an iron-containing pigment. The abundant siderosis causes the macroscopic appearance of tobacco-colored nodules ("Gamna's nodules"). In his cases, he did not observe any changes of the liver nor ascites. Splenectomy was followed by apparent recovery in five cases.

K. SCHULHOF.

RARE MALFORMATION OF KIDNEY. F. DE GAETANI, Arch. per le sc. med. **49**:138, 1927.

The anomaly was found in an infant, aged 41 days, who died of capillary bronchitis. The author believes that the lateral torsion, especially of the left

kidney, was greater in his case than in any other described before. The lower part of the hilum was turned laterally. Besides this, both kidneys were hypertrophic, lobated and slightly ectopic and the renal blood vessels anomalous.

K. SCHULHOF.

CALCIFYING FOCAL BRONCHOPNEUMONIA. A. FABRIS, Arch. per le sc. med. **49**: 201, 1927.

The patient had been operated on for cancer of the breast and had died of bronchopneumonia. She also had a fracture of the femur. The alveolar septums of the lungs, bronchi and the tunica media and interna of the small blood vessels were infiltrated with calcium salts. The author claims that no other case of similar lime metastasis had been described so far in the Italian literature.

K. SCHULHOF.

METACHROMATIC SUBSTANCE IN WALL OF BLOOD VESSELS. M. C. BERNARDO, Arch. per le sc. med. **49**:220, 1927.

Bernardo stained arteries with cresyl violet R, as recommended by A. Schultz. She observed constantly in syphilitic aortitis in young subjects a metachromasia (scarlet red color) of the intima of the vasa vasorum. This feature was absent in normal and in arteriosclerotic vasa vasorum. The metachromasia of the media was as a rule more pronounced than in normal and in arteriosclerotic controls. It was constant in the cerebral arteries in general paralysis and in the renal arteries in syphilitic nephrosclerosis. Senile dilatation of the aorta occurs without metachromasia.

K. SCHULHOF.

DEGENERATIVE CHANGES AND FUNCTIONAL ALTERNATION IN PARENCHYMA OF LIVER. A. MUGGIA, Arch. per le sc. med. **49**:225, 1927.

The author injected rats simultaneously with methylene blue and various poisons. Different parts of the liver stained unequally. He found the gravest degenerative changes in those cells of the liver, which contained methylene blue. He concludes that this is evidence proving the theory that parts of the liver alternate in the function, and that those parts that are active at the time of the poisoning are the ones that are gravely affected.

K. SCHULHOF.

EXPERIMENTAL HYPERCHOLESTEROLEMIA AND VASCULAR CHANGES. M. THÖLLDTE, Beitr. z. path. Anat. u. z. allg. Path. **77**:61, 1927.

The frequently investigated question of the relation of hypercholesterolemia to atherosclerosis is still the subject of controversy and of experimental research. So long ago as 1914, Anitschkow had stated that it is necessary to distinguish two forms of atherosclerosis brought about experimentally in the rabbit, an epinephrine or mechanical type and a cholesterol or toxic type. More recently (1922, 1925), Schmidtmann had claimed that cholesterol feeding which leads to hypercholesterolemia in the rabbit is associated with an increase in blood pressure which runs parallel to the increased cholesterol content of the blood, and that atherosclerosis results only when the hypercholesterolemia is associated with increased blood pressure. She ascribed the hypertension to an epinephrine-like or synergistic action of the cholesterol. Thölldte reinvestigated this subject. He criticizes Schmidtmann's weekly blood pressure readings, claiming that such infrequent measurements do not give a true pressure curve. In his experiments the blood pressure was read daily during the control period and twice daily during the period of cholesterol feeding, the latter consisting of cholesterol in linseed oil. The experiments had a duration of from 121 to 423 days, and the total amount of cholesterol fed varied from 52 to 211.5 Gm. No changes in blood pressure, greater than the normal physiologic variations, were noted in these protracted experiments. The cholesterol content of the blood

began to increase on the tenth to seventeenth day after the beginning of cholesterol feeding, and reached its highest point of more than fifteen times the original value on the one hundred and sixth to the one hundred and forty-fifth day. After maintaining the maximum level for a few days, a progressive decrease in blood cholesterol occurred, until a level of from two to three times the original normal value was reached, at which point the figures remained constant. With the decrease in cholesterol content of the blood the gross lipemia of the serum disappeared. Although no increase in blood pressure was noted by Thölldte, marked atherosclerosis of the aorta was present, and similar changes were seen also in the veins, in which the pressure is low.

O. T. Schultz.

Rudimentary Appendicitis. L. Aschoff, Beitr. z. path. Anat. u. z. allg. Path. **77**:141, 1927.

Aschoff devotes the first part of his contribution to vigorous protest against Ricker's conception that the primary factor in the pathogenesis of appendicitis is a circulatory disturbance which leads to necrosis, and against Rössle's contention that the appendix normally undergoes active peristaltic contractions, absence of which predisposes to infection. One of the advantages of being editor of a journal in which the editor's adversaries publish their contributions is that the editor may have the last word, even on so old a subject as the pathogenesis of appendicitis. Aschoff maintains his previously expressed opinion that appendicitis results from the prolonged contact of certain pathogenic bacteria with the mucosa, the retention being favored by the normal contractures of the appendix and by the furrows in its mucosa. He does not deny the occurrence of peristaltic activity, but claims that this is so slight as to have no effect in causing either circulatory disturbances or infection. Aschoff next proceeds to a discussion of a previously published observation of one of his students concerning the apparently normal appendix removed in the course of other abdominal operations, for which Aschoff's term "stolen appendix" appears to correspond to our "prophylactic appendix." In some of such apparently normal appendixes Brauch had described the presence of a few leukocytes in the muscle coats. He had considered the process a physiologic one. In a further series of appendixes from cases of so-called chronic appendicitis and of apparently normal "stolen appendixes," Aschoff detected similar changes in a fair proportion. He concludes that the presence of a few leukocytes in the muscle coats is not physiologic, but is the result of a mild, true inflammatory process, which he terms rudimentary appendicitis. In two such appendixes serial sections revealed the area of primary mucosal involvement. He believes that mild, acute inflammation of the appendix is more common than is generally believed to be the case, and that the process frequently heals without the development of clinical symptoms.

O. T. Schultz.

Osteosclerotic Anemia. M. B. Schmidt, Beitr. z. path. Anat. u. z. allg. Path. **77**:158, 1927.

To a number of *Ziegler's Beiträge* issued as a Festschrift for Paul Ernst, M. B. Schmidt contributes a detailed histologic study of the bone and marrow of a case of osteosclerotic anemia and a discussion of the possible relations of this condition to infantile Albers-Schönberg marble bone disease. Schmidt's patient was a man who died at the age of 56 years. Pallor was noticed first in 1924. In June, 1925, the erythrocyte count was 2,900,000; hemoglobin, 40 per cent; leukocytes, 3,000, and color index, 0.61; a few megaloblasts and many normoblasts were present. During the last admission, from January to June, 1926, the erythrocyte count had decreased to 1,500,000; hemoglobin, from 30 to 28 per cent; leukocytes, from 3,200 to 2,500, and color index, 1.0; during this time there were no abnormal red or white cells. The spleen was enlarged.

The hypophysis was slightly increased in size, but was normal microscopically. On microscopic examination there was found in the skeleton a generalized condition of replacement of the fatty and hemopoietic marrow of the spongiosa of the bones by rather firm fibrous tissue, in which moderate new formation of bone had occurred; the original bone trabeculae were increased in thickness. The cortical bone did not show any changes. The anemia, of secondary and later of aplastic type, was ascribed to the fibrous replacement of marrow, and the condition is considered a system disease involving the marrow and leading to disturbance of both its osteogenic and hemopoietic functions. Albers-Schönberg disease occurs in children, and is characterized by increased bone formation and greater density of the bones with a tendency to spontaneous fracture, and by the absence of anemia. As a second type of this disease Assmann had described a condition in which the changes in the bone were similar, but were accompanied by secondary anemia. The latter form, which had been termed osteosclerotic anemia, occurs in both adults and children. Schmidt thinks that the fact that his patient was free of symptoms until two years before death speaks against the view that the osteosclerotic form with anemia is the end-stage of Albers-Schönberg disease arising in childhood.

O. T. Schultz.

The Hardness of Bone. R. Rössle, Beitr. z. path. Anat. u. z. allg. Path. **77**: 174, 1927.

Rössle adopted the Brinnell method of testing hardness for determining the hardness of bone, the scratch method being found less satisfactory. The compact portion of the diaphysis of the femur was used for study. Bone hardness was found to bear a relation to the specific weight of the bone, but not to its calcium content. The bone of young children is softer than that of adults, but the normal degree of hardness of adult bone is attained early with the lamination of the compact layer. Senile bone retains the normal hardness, even when marked osteoporotic atrophy is present. Pathologic increase in hardness was not detected in any condition; decrease in hardness occurred in local and general destructive diseases of bone.

O. T. Schultz.

Metastatic Sarcoma of the Iris. E. von Hippel, Beitr. z. path. Anat. u. z. allg. Path. **77**:209, 1927.

Metastatic intra-ocular sarcoma is less frequent than secondary carcinoma, of which about 100 cases are recorded in the literature. Von Hippel could find reported in the literature only nine cases of metastatic sarcoma involving the iris and ciliary body, two of which were not subjected to anatomic examination. In four a pigmented tumor of the skin was the primary seat, in two a tumor of the mediastinum, in one a sarcoma of the mammary gland, in one the sheath of the optic nerve, and in one the primary tumor was not stated. In 1926, Elsching reported, as the first case arising from a sarcoma of an internal organ, a sarcoma of the uvea secondary to sarcoma of the ovary. Von Hippel adds a tumor of the iris and ciliary body of a child, aged 10 months. The posterior portion of the eye was not involved. The primary tumor was an obstructing round cell sarcoma of the pylorus, itself a rare type of tumor, especially at so early an age.

O. T. Schultz.

Phlorhizin Necrosis of the Liver. F. Fischler, Beitr. z. path. Anat. u. z. allg. Path. **77**:217, 1927.

The increased susceptibility of the liver to toxic agents during starvation is well known. Fischler describes the occurrence of necrosis of the liver in rabbits rendered glycoprivic by starvation and phlorhizin. Some animals received in addition epinephrine, with the object of increasing sugar mobiliza-

tion. In one series of starved phlorhizinized rabbits the common duct was ligated to increase the damage to which the liver might be subjected by disturbed function, and one starved phlorhizinized rabbit with the common duct ligated received epinephrine. Six of the starved animals that received phlorhizin alone were saved by means of injections of dextrose. In nine (75 per cent) of twelve experiments successfully carried to completion, necrosis of the liver was noted. The necroses were central in origin, often occupied several lobules, and bore a striking resemblance to those of eclampsia; some were hemorrhagic and in others leukocytic infiltration was present. Deprivation of carbohydrate and reduction in the glycogen content of the liver apparently render this organ susceptible to toxic materials which it handles without damage under normal conditions.

O. T. SCHULTZ.

ORIGIN OF HYALIN AND AMYLOID. H. LOESCHCKE, Beitr. z. path. Anat. u. z. allg. Path. **77**:231 (1927).

Starting with the assumption that the body produces precipitating antibodies against its own degraded proteins, Loeschcke explains hyaline degeneration of fibrous tissues as the result of local precipitation in the tissues in which there occurs a cyclic destruction of protein, as in the ovary, mamma, and axillary apocrine sweat glands, or progressive slow destruction, as in arteriosclerosis with a consequent decrease in the blood supply. Amyloid is explained as a local precipitation of leukocytic antigen, the localization of the deposition being due to the site of formation of antibody in the cells of the reticulo-endothelial system.

O. T. SCHULTZ.

DICEPHALY. G. B. GRUBER and H. EYMER, Beitr. z. path. Anat. u. z. allg. Path. **77**:240, 1927.

Gruber and Eymer record an anatomic study of six examples of dicephaly with varying degrees of reduplication of the vertebral column. The degree of reduplication of the internal organs depends on the extent of duplication of the vertebral column. Heubner had claimed that every dicephalic monster has a double respiratory system; this was not true of the first case in the present series. In one case with doubling only of the cervical vertebral column, four phrenic nerves had been formed. The position and shape of the internal organs is influenced by the space available for them during the developmental period. The contribution is embellished by a reproduction of an illustration of an adult dicephalic Turkish soldier, dated 1697, and that of a dicephalic child, dated 1512.

O. T. SCHULTZ.

JUVENILE HYPERTROPHIC PERIOSTITIS. H. HOLTHUSEN, Beitr. z. path. Anat. u. z. allg. Path. **77**:318, 1927.

Holthusen describes differences, as determined roentgenologically, in the hypertrophic periostitis or hypertrophic pneumic osteo-arthropathy of Bamberger-Marie of young growing children as compared with adults. In the latter the periosteal thickening predominates over bone formation, whereas in juveniles, in whom bone formation is still active, a greater degree of periosteal bone formation occurs. Holthusen's patient was a girl, aged 18, with marked evidences of infantilism.

O. T. SCHULTZ.

TUMOR OF THE ENDOCARDIUM. A. BINDER, Beitr. z. path. Anat. u. z. allg. Path. **77**:332, 1927.

A soft polypoid tumor the size of a hen's egg was found in a woman who died at the age of 45 years; it was attached by means of a narrow pedicle to

the auricular septum and projected into the left auricle. It was composed of gelatinous mucoid tissue and contained blood vessels whose endothelium was continuous with that covering the mass, a point which leads Binder to conclude that the structure was an organized thrombus rather than a neoplasm.

O. T. SCHULTZ.

HYALINE BODIES IN A LYMPHOGRANULOMA OF THE STOMACH. C. FROBOESE, Beitr. z. path. Anat. u. z. allg. Path. **77**:363, 1927.

A superficially ulcerated, nodular lesion of the stomach, obtained at operation, had the characteristic histology of Hodgkin's lymphogranuloma. In addition to the usual cellular elements it contained large numbers of acidophilic hyaline bodies. Some of these were small and intracellular, others were large and extracellular. The material stained deeply by the Weigert myelin method, an indication of its lipoid nature. After prolonged discussion and debate of all the possibilities relating to the formation of hyaline bodies, the author concludes that they are formed within histiocytes, and that their presence is an indication of the protective function of these cells, which take up and store noxious substances and by intracellular synthesis transform the latter into harmless materials which manifest themselves morphologically as so-called hyaline bodies.

O. T. SCHULTZ.

HYPOPLASIA OF THE KIDNEY. R. HANSER, Beitr. z. path. u. z. allg. Path. **77**: 417, 1927.

The left kidney apparently was absent in a man who died at the age of 53. The left ureter opened normally into the bladder; at its upper end was a rudimentary pelvis which was capped by a small amount of tissue. The left renal artery and vein were absent. Thorough microscopic examination of the tissue which represented the left kidney failed to reveal any glomeruli. A small number of epithelial lined tubules were embedded in fibrous tissue. On the basis of this case and of the previous literature, Hanser enters into a discussion of the differential diagnosis of unilateral aplasia and hypoplasia of the kidney. He concludes that even the most careful microscopic study will not at times permit an absolutely certain decision as to whether a rudimentary kidney has resulted from aplasia or hypoplasia. He interprets the tubules present in his own specimen as derivatives of the renal blasteme and therefore decides that his is an example of hypoplasia.

O. T. SCHULTZ.

CROSSED DYSTOPIA OF THE THYMUS. P. SCHNEIDER, Beitr. z. path. u. z. allg. Path. **77**:449, 1927.

Developmental anomalies of the thymus are rare. Schneider briefly reviews the previously recorded examples and describes, as a condition not previously noted, crossed dystopia of the thymus in a boy, aged 11. From the normally situated upper cervical portions the larger lower portions of the two lobes crossed each other, the main portion of the left lobe lying anteriorly and on the right side, and the right lobe on the left side.

O. T. SCHULTZ.

PATHOLOGIC HISTOLOGY OF LEONTIASIS OSSEA. H. MARX, Beitr. z. path. u. z. allg. Path. **77**:501, 1927.

Marx describes in detail the microscopic anatomy of portions of bones removed from a case of leontiasis ossea. The bone consisted of a diffuse mixture of osseous trabeculae and fibrous tissue. The latter in places was cellular and appeared to be in active growth. New bone formation and bone resorption were active. Resportion occurred by means of osteoclasts and was lacunar in type. Bone formation occurred by direct transformation and calcification of

the newly formed fibrous tissue, both by direct apposition on older bone trabeculae and within masses of fibrous tissue without the presence of osteoblasts or osteoid tissue. The newly formed bone was vascular. Those areas in which the process had apparently come to rest were composed of irregular trabeculae of bone which enclosed islands of dense fibrous tissue. The pathologic process with which that described is most similar is osteitis fibrosa, which differs, however, from leontiasis in the formation of osteoid tissue and in the relatively avascular condition of the bone which is formed. Although there may be considerable similarity in the two processes, Marx concludes that true leontiasis ossea is a distinct disease.

O. T. SCHULTZ.

EFFECT OF ROENTGEN RADIATION ON THE KIDNEY. G. DOMAGK, Beitr. z. path. u. z. allg. Path. **77**:525, 1927.

Domagk devotes fifty-one pages to an experimental study of the effect of roentgen irradiation on the kidney of the rabbit. The work had its inception in a fatal chronic interstitial nephritis which followed the therapeutic irradiation of the abdomen of a girl, aged 9, for tuberculosis mesenteric lymphadenitis. The earliest changes noted in the rabbit's kidney were clumping and disappearance of the cytoplasmic rods and distortion of the mitochondrial apparatus of the convoluted tubular epithelium. These alterations increased progressively with the duration after an adequate dosage of radiation, and, after some time, led to atrophy and destruction of the tubular epithelium and to the presence of casts within the tubules. These tubular changes are the result of colloid chemical alterations which lead to swelling and partial coagulation of the cytoplasm. The glomeruli were relatively resistant and showed only congestion. With the passage of time the injured tubules were replaced by fibrous tissue which was often infiltrated by lymphocytes. The end-result was a small, contracted, granular kidney. The nitrogen content of the urine was increased as the result of water retention. Marked decrease in weight which followed irradiation in some of the animals was held to be due to destruction of protein and not to loss of water. Decrease in concentrating power of the kidney was noted in some of the animals and a few developed anuria. Animals maintained on a diet high in protein and low in water showed more marked changes than those kept on normal diet.

O. T. SCHULTZ.

RUPTURE OF A DIAPHRAGMATIC HERNIAL SAC. J. LÜNING, Centralbl. f. allg. Path. u. path. Anat. **40**:97, 1927.

An apparently normal male child 3 days old died suddenly after marked dyspnea. At the autopsy the diaphragm in the left tendinous part contained a smooth-edged opening 3.5 by 2.5 cm., through which a goose-egg sized sac protruded that was lined with peritoneum and filled with everything in the peritoneal cavity except the liver, 5 cm. of ileum, the first part of the ascending colon and the rectum. Two tongue-like projections, the largest 25 by 20 by 4 mm., extended from the left lobe of the liver into the sac. A recent tear in the sac 5 cm. long with blood-stained edges permitted several loops of small bowel to enter the left pleural cavity. The left lung was atelectatic, and the mediastinum displaced to the right of the midline. Presumably the hernial sac burst after the stomach was distended with food.

GEORGE RUKSTINAT.

THE PATHOLOGY OF APOPLEXY. K. WESTPHAL and R. BÄR, Deutsches Arch. f. klin. Med. **151**:1, 1926.

At autopsy pure cerebral hemorrhage, combinations of anemic necrosis and bleeding in a single focus, and separated foci of anemic necrosis and bleeding in the same brain were noted. In the bloody softened foci and their immediate vicinity there occurred a variable but usually widespread necrosis of arteries,

arterioles, capillaries and veins independent of arteriosclerosis in the brain vessels. Bleeding occurred from many vessels, occasionally from the so-called miliary aneurysms of Charcot, at times from apparently uninjured vessels, and many foci showed at their edge that they consisted of numerous small bleeding places. The occurrence of white and red softening in one spot and again separated in the same brain indicated a common origin for both. Apoplexy without demonstrable anatomic changes was thought due to sudden anemia of parts of the brain due to angiospasm or to arteriosclerotic functional disturbances.

GEORGE RUKSTINAT.

ON THE HISTOPATHOGENESIS OF PERTHES' DISEASE, ON THE BASIS OF AN EARLY CASE. KARL ROCKEMER, Frankfurt Ztschr f. path. **35**:1, 1927.

The histologic changes in an early case of Perthes' disease are described. There was an almost complete necrosis of the spongy bone of the head of the femour although the articular cartilage was still supported by it. Furthermore the spongy part of the head had been the site of a pathologic impression fracture. Evidence of repair could not be demonstrated in the early stage of the disease.

Rockemer points out that in this and a number of other cases of Perthes' disease the changes are in agreement with those seen in Köhler's disease of the head and of the second metatarsus. He attempts to decide the pathogenesis of Perthes' disease on the basis of the histologic picture, and thinks it probable that a disturbance of nutrition lies at the basis of the disease made possible by the special nutritive conditions for the head of the femur. The nutritive disturbance in most cases is brought about by trauma.

E. M. HALL.

FREE TRANSPLANTATION OF THE UPPER EXTREMITY THROUGH AMNIOGENIC MALFORMATION. L. HIRSCH and H. REINECK, Frankfurt Ztschr. f. Path. **35**:48, 1927.

The authors cite a case of extreme malformation in a new-born child in which there had been a transplantation of the left upper extremity to the lower part of the left trunk. They believe that an anomaly of the amnion effected a free transplantation of the "anlage" of the extremity. As proof of this they call attention to a demonstrable scar at the shoulder at the usual location of the arm and also to the peculiar innervation of the limb. Instead of segments C4 to D1 of the plexus brachialis supplying the part, the nerves are derived from segments D9 and 10. Furthermore, the scar in the skin on the left shoulder convexity shows visible patterns which correspond closely to the bone-building part on the head of the misplaced humerus. For these reasons the authors consider that the arm was originally formed in the normal place.

E. M. HALL.

ELECTIVE FATTY DEGENERATION OF THE ISLANDS OF LANGERHANS IN ACUTE PANCREATITIS WITHOUT DIABETES. LUDWIG KOCH, Frankfurt Ztschr. f. Path. **35**:107, 1927.

The author cites a case of acute pancreatitis which developed in a very fat woman, aged 60, who had gallstones. The illness was of five days' duration. The head and half the body of the pancreas were intact the remaining portion showed hemorrhage, necroses and fat necrosis. In this part the cells were all destroyed while in the better preserved part the islands of Langerhans show a marked fatty degeneration. Sugar did not appear in the urine. The author thinks that the island hormone is contained in the remaining organs of the body in amounts sufficient to prevent glycosuria over a short period.

E. M. HALL.

ASCARIS IN FALLOPIAN TUBE. H. HOFSTÖTTER, Wien. klin. Wchnschr. **40**:878, 1927.

An ascaris parasite was found in the left tube in a pregnant woman who died from peritonitis, presumably from perforation of the intestine by the parasite.

PERIARTERITIS NODOSA. P. KIMMELSTIEL, Virchows Arch. f. path. Anat. **265**: 16, 1927.

The author reports a microscopic study of four cases of periarteritis nodosa, in three of which only microscopic changes were detectable. The arterial lesion was characterized by medial degeneration, intimal proliferation, and adventitial round cell proliferation, none of which processes bears any secondary relation to any of the others, all being the result of the primary incitant. The latter is probably an allergic condition of the arterial system. The discussion relates chiefly to an evaluation of the relation of the nerve changes and the interstitial myocarditis noted in three cases to the arterial involvement. The three conditions are held to be the result of the same noxious agent.

O. T. SCHULTZ.

OBLITERATIVE HEPATIC ENDOPHLEBITIS. S. GÁSPÁR, Virchows Arch. f. path. Anat. **265**:31, 1927.

In a girl, aged 18, the liver was the seat of a widespread endophlebitic process which involved the small as well as the large branches of the hepatic veins. Although such a process in the smaller branches has usually been looked on as secondary to thrombosis of the larger veins due to endophlebitis, Gáspár believes that the inflammatory process in his case involved primarily the smaller veins as well as the larger ones as the result of a perivascular syphilitic process which led to the formation of miliary gummas in the adventitial tissue.

O. T. SCHULTZ.

THE EFFECT ON THE LIVER OF EXPERIMENTAL OBSTRUCTIVE JAUNDICE. L. LOEFFLER, Virchows Arch. f. path. Anat. **265**:41, 1927.

Loeffler criticizes previous work, the aim of which has been the elucidation of the sequence of events that lead to the changes which result from experimental ligation of the common duct, in that the attention has been focused on the parenchyma of the liver rather than on the liver as a whole. Working with rabbits, he studied the circulation of the liver in vivo by the method of capillary microscopy at various, and especially early, periods after ligation of the ducts, and correlated the circulatory changes with the histologic ones. He insists that retention of bile does not render the liver cells free from fat or glycogen, that it does not cause disappearance or necrosis of liver cells, that it does not stimulate the bile ducts or connective tissue to proliferation, and that it does not cause leukocytic or monocytic infiltration of the damaged liver tissue. All of these changes, which are the ones uniformly described as following ligation of the duct, are the result of the action of the bile on the nervous and circulatory mechanisms of the liver, to disturbances of which the parenchymatous and interstitial changes are secondary.

O. T. SCHULTZ.

REDUPLICATION OF THE GALLBLADDER. A. PRIESEL, Virchows Arch. f. path. Anat. **265**:76, 1927.

Reduplication of the gallbladder of the human being is extremely rare, although of more frequent occurrence in lower animals, especially the cat. Priesel describes a double gallbladder observed by chance during postmortem examination of a man, aged 54. The two bladders were covered by a common peritoneal membrane, within which the two structures were complete, each hav-

ing its own mucosa, fibrous layer and muscle coat. Each opened by a separate cystic duct into the single common duct. The contents of the more mesial gallbladder were thicker than those of the lateral one, due to a greater degree of kinking of the duct. Inflammatory changes were not present. The condition is believed to have resulted from longitudinal division of the original gallbladder anlage.

O. T. SCHULTZ.

CHANGES IN THE DUODENAL MUCOSA IN PEPTIC ULCER. H. PUHL, Virchows Arch. f. path. Anat. **265**:160, 1927.

Much attention has been paid by many different writers to the pathologic changes in the nonulcerated gastric mucosa associated with peptic ulcer. Much less attention has been paid to similar changes in the duodenal mucosa. Acute catarrhal duodenitis, fresh superficial erosions, and the scars of healed erosions or shallow ulcers are frequently associated with duodenal ulcer. Erosion or ulceration frequently does not extend entirely through the Brunner's gland layer, and healing occurs readily, with the formation of a thin mucosa which covers a gland layer of decreased thickness in which connective tissue is increased. Chronic inflammation which extends to the muscularis mucosae may lead to obstruction of the deeper gland lobules, resulting in cystic dilatation, atrophy, and final replacement by fibrous tissue. By the regenerative changes which occur over erosions and in the chronically inflamed duodenal mucosa, the latter may be transformed into a mucosa with long slender villi like those of the lower small intestine. In the healing process of chronic ulcers, epithelial metaplasia occurs, as well as other alterations, which Puhl believes have been described by others as early malignant changes.

O. T. SCHULTZ.

ALEUKEMIC LYMPHADENOSIS OF THE PHARYNX. W. ANTHON, Virchows Arch. f. path. Anat. **265**:199, 1927.

A man, aged 63, when first seen had a chronic ulcer of the left tonsil. Slight generalized lymphadenopathy had been present for three years. Microscopic examination of the removed tonsil led to a doubtful diagnosis of atypical hyperplastic tuberculosis. Five months later there was difficulty in swallowing, and the lymphoid tissue of the pharynx and nasopharynx was found greatly hyperplastic and superficially ulcerated. The leukocyte count varied from 2,900 to 3,600, with 27 to 43 per cent lymphocytes and 6 to 13 per cent monocytes. The course of the condition was progressively downward and ended in death. At necropsy there was found generalized hypertrophy of the lymphoid tissues, the process being most marked in the pharynx. On microscopic examination the hyperplastic lymphoid tissue consisted of large endothelioid cells, eosinophils and Sternberg giant cells, and presented a picture suggestive of lymphogranulomatosis. The latter condition was excluded by the absence of fibrosis, and the author concludes that the process was an aleukemic lymphadenosis.

O. T. SCHULTZ.

EFFECT OF TOXINS ON MYELOPOIESIS AND ON THE RETICULO-ENDOTHELIAL SYSTEM. OLGA BYKOWA, Virchows Arch. f. path. Anat. **265**:226, 1927.

Guinea-pigs received single large and repeated small injections of defibrinated scarlet fever blood, scarlet fever toxin, or diphtheria toxin, and rabbits were similarly injected with diphtheria toxin or suspensions of diphtheria bacilli. A marked reaction on the part of the reticulo-endothelial system occurred, characterized by mobilization of cells and phagocytosis. Single large doses caused nuclear degenerative changes in these cells and the deposition of lipoids in the cytoplasm. Repeated small doses resulted in myelopoiesis in the spleen, lymph nodes, liver, suprarenals and bone marrow. Reticulo-endothelial changes were greatest in the spleen, lymph nodes and liver, the myelopoietic changes in the bone marrow and spleen. The reactions noted appeared to be the result of the dosage and duration of action of the injected material, rather than of its nature.

O. T. SCHULTZ.

HISTOLOGIC OBSERVATIONS ON THE GASTRO-INTESTINAL TRACT OF ARTHROPATHS, NEPHROPATHS AND CARDIOPATHS. O. HOLSTI, Arb. a. d. path. Inst. zu Helsingfors **4**:415, 1926.

The gastro-intestinal tracts of nine persons dying accidentally were used as a criterion of normal. Material from fifteen arthropaths, nephropaths and cardiopaths and from thirteen people dying of other diseases was studied and the following observations were made. In healthy people inflammatory processes in the gastro-intestinal tract are uncommon although venous, subintimal fibrous connective changes occur early. Inflammatory, regressive or cirrhotic processes are the rule in death from some disease. In the acute phase of arthropathies, etc., the inflammatory lesions are usually more intense than at other times, but in one instance they were entirely lacking. Chronic lesions are variable even in the same illness, and range from regressive changes in the parenchyma and slight proliferations of the connective tissue to inflammatory processes of all degrees. Arteriopathies are more common in the group of arthropaths, nephropaths and cardiopaths. The inflammatory lesions in this group were for the most part fresh secondary processes. Older lesions seemed to antedate both the arthropathy illness or infection of the upper respiratory tract, where such existed.

GEORGE RUKSTINAT.

HEPATOLENTICULAR DEGENERATION. A CLINICAL, ANATOMIC AND EXPERIMENTAL STUDY. IVAN MAHAIM, Schweiz. Arch. f. Neurol. u. Psychiat. **16**:283, 1927.

In these experiments dogs received injections of 50 per cent alcohol in doses of 40 cc. through the biliary passages and died with intense icterus after progressive cachexia. The liver showed marked changes in the hepatic cells with biliary pigmentation and some inflammatory reaction. The brain showed alterations of the nerve cells, especially in the cortex, and vascular and glial changes of the central nuclei, chiefly of the thalamus and the caudate nucleus. The lesions of the nerve cells were regarded as a general reaction and those of the vessels and the neuroglia as more specific reactions of the central nuclei.

CHANGES IN THE NERVES IN THE WALL OF THE STOMACH IN CHRONIC GASTRIC ULCERS. HARALD OKKELS, Acta path. et microbiol. Scandinav. **4**:89, 1927.

Nerves are frequent near gastric ulcers, and they are often the seat of perineuritis from the ascending lymphangitis. Central cicatricial neuromas may develop in the nerves themselves. The perineuritis and the inclusion of nerves in dense fibrous tissue may explain the pain in gastric ulcer.

Pathologic Chemistry

DETERMINATION OF UREA BY GASOMETRIC MEASUREMENT OF THE CARBON DIOXIDE FORMED BY THE ACTION OF UREASE. D. D. VAN SLYKE, J. Biol. Chem. **73**:695, 1927.

Methods are described for rapid determination of urea in blood and urine by measuring in the manometric blood gas apparatus the carbon dioxide of the ammonium carbonate formed by action of urease. The blood urea may be determined in either whole blood, serum, or Folin-Wu filtrate. Microdeterminations may be performed with 0.2 cc. of blood.

AUTHOR'S SUMMARY.

SOME EFFECTS OF ASPHYXIA ON BLOOD CHEMISTRY. J. B. COLLIP, J. Biol. Chem. **74**:28, 1927.

Asphyxia produces a definite decrease in the plasma volume and p_H of fetal blood. These changes are accompanied by an increase in blood calcium and a decrease in inorganic phosphorus content.

ARTHUR LOCKE.

INFLUENCE OF FAT AND CARBOHYDRATE DIETS UPON THE LEVEL OF BLOOD URIC ACID. V. J. HARDING, K. D. ALLIN and B. A. EAGLES, J. Biol. Chem. **74**:631, 1927.

The increase in blood uric acid observed in persons on high fat diets is correlated with decreased excretion. Low protein-high carbohydrate diets of mixed origin fail to raise the level of blood uric acid in the normal puerperium. Similar diets showed raised blood uric acid in the puerperium following toxemia.

AUTHORS' SUMMARY.

RESEARCHES ON THE ANTICOAGULANT SUBSTANCES OF THE BLOOD. M. DOYON, Le Sang **1**:13, 1927.

The blood owes its fluidity to an anticoagulant substance elaborated in the organism. In normal blood, this substance is hardly measurable. After injection of peptone, the amount of the anticoagulant substance increases considerably. In certain animals and probably also in man, the substance appears to be secreted chiefly by the liver; on removal of this organ, the peptone ceases to act. Other organs supplement the secretion to a certain extent. The activity of the anticoagulant substance in the organs is masked by the presence of coagulant substances. The anticoagulant substance originates in the nuclear bodies of the cells. It may appear at the stage of nucleoproteid, nuclein, nucleic acid or nucleotid. The author details the chemical properties of this anticoagulant substance. About 0.005 Gm. of the latter prevented coagulation of 250 Gm. of blood, for from thirty to forty minutes.

R. LAPIDUS.

THE PRESENCE OF IODINE IN HUMAN AND ANIMAL ORGANS. E. MAURER, H. DUCRUE and W. PALASOFF, München. med. Wchnschr. **74**:271, 1927.

The average iodine content of the organs of six women was determined shortly after postmortem examination. The hearts contained 0.0526 mg.; the livers, 0.0566 mg.; the spleens, 0.061 mg.; the suprarenal glands, 0.112 mg., and the ovaries, 0.741 mg. per hundred grams of tissue. The average values for twelve fetuses were: hearts, 0.012 mg.; livers, 0.017 mg.; spleens, 0.029 mg.; thymus glands, 0.046 mg.; ovaries, 0.138 mg., and thyroid glands 0.25 mg. In the ovaries of swine there was an average of 0.648 mg. of iodine per hundred grams of tissue; in those of cattle, 0.609 mg.

J. W. WILLEMS.

Microbiology and Parasitology

THE PATHOGENIC RÔLE OF TRICHOCEPHALUS DISPAR (Trichuris Trichiura). M. FERNÁN-NÚÑEZ, Arch. Int. Med. **40**:46, 1927.

Trichocephalus dispar, a cosmopolitan intestinal parasite, is of great pathologic importance, and has not been adequately studied. In the Magdalena River valley of Colombia, 92 per cent of 1,336 persons examined had intestinal parasites, of which 41 per cent were *Trichocephalus dispar*. Sixty-two per cent of sixteen autopsies on persons who had died from various causes in Colombia showed *Trichocephalus* infestation, with localization in the cecum, appendix, hepatic and splenic curvatures of the colon, sigmoid and rectum. The subcutaneous injection of eggs of *Trichocephalus despressisunculus* into puppies produced an infection of the intestinal tract with appearance of ova in the feces. *Trichocephalus dipar* is a definite cause of appendicitis. Many cases of so-called tropical "idiopathic peritonitis" are of helminthic origin. *Trichocephalus* is a factor in the transmission of infections through the intestinal tract, due to its tendency to perforate the intestinal wall, resulting in peritonitis, septicemia, perinephritis and pyelitis. Approximately 30 per cent of cases commonly diagnosed as amebic dysentery

in tropical America are of trichocephalic origin. Anthelmintic treatment is specific in such cases. Purpura hemorrhagica can result from intoxication with the hemolytic enzymes injected in the host by *Trichocephalus*. Acrocyanosis dystrophica, pernicious anemia, urticaria and goiter may be associated with helminthic infestation. The blood pigment in the intestinal mucosa of *Trichocephalus dispar* is human pigment, as can be demonstrated by a modification of the Teichman test. Eosinophilia is commonly more constant and of higher degree in trichocephalic infection than in that produced by other nematodes, indicating that the small number of trichocephali which are usually found are capable of intoxicating the host more than are the usually large number of other helminths. *Trichocephalus* is associated with the hookworm in 33 per cent of all cases (in the tropics). As the treatment for hookworm given by mouth is often ineffective against *Trichocephalus*, the campaigns against hookworm are not entirely effectual unless attention is given to the elimination of *Trichocephalus*. If it is not eliminated, its symptoms may be attributed to the hookworm. This oversight has been one of the causes why *Trichocephalus* has not received the study that it deserves.

AUTHOR'S SUMMARY.

LOCAL PROGRESSION WITH SPONTANEOUS REGRESSION OF TUBERCULOSIS IN THE BONE MARROW OF RABBITS, CORRELATED WITH A TRANSITORY ANEMIA AND LEUCOPENIA AFTER INTRAVENOUS INOCULATION. CHARLES A. DOAN and FLORENCE R. SABIN, J. Exper. Med. **46**:315, 1927.

With massive intravenous injections (from 1 to 2 mg.) of bovine tubercle bacilli in rabbits there is a marked involvement of the bone marrow in the early acute phase. This reaction is initiated on the eighth to tenth days by the development of large numbers of young monocytes in situ. From the twelfth to the twentieth day, approximately, there is an increasing development in bone marrow of typical tubercular tissue, epithelioid cells and giant cells of the Langhans type, many showing tubercle bacilli. This new growth eliminates the normal fat cells and encroaches on and depresses the hemopoietic foci. The bone marrow always tends toward spontaneous healing provided the animals survive the first acute reaction sufficiently long. The method of healing involves a rapid disintegration of the epithelioid cells without caseation and the phagocytosis of debris by the clasmatocytes. The extent and progress of the tuberculosis of the marrow are accurately reflected in the peripheral blood by a decrease of platelets, an anemia and a fall in the granulocytic leukocytes. The onset of the recovery is initiated by the return of the platelets to normal, by a rise in hemoglobin, followed quickly by a rise in red cells, and by a more gradual increase in the granulocytes. During the third month, and after, there is a hyperplasia of the blood-forming elements in the bone marrow with a rise in the peripheral blood of the red cells, hemoglobin and the granulocytes above their original levels. The bone marrow becomes entirely normal when the animal survives beyond 100 days, regardless of a steadily progressing, extensive tuberculosis elsewhere. The varying length of survival in this series of rabbits under uniform environmental conditions, and infected with the same dosage of the same strain of organism, tends to emphasize the importance of the factor of individual resistance of the host in susceptibility to infectious disease.

AUTHORS' SUMMARY.

NATURE OF THE TOXIC MOIETY OF STREPTOCOCCUS SCARLATINAE. CHARLES W. DUVAL and R. J. HIBBARD, J. Exper. Med. **46**:379, 1927.

Further evidence is presented in support of the view that the poisonous substance of the scarlatinal streptococcus is derived from the bacterial cell through dissolution of its plasm.

STREPTOCOCCUS BACTERIOPHAGE. GEORGE SHEVARTZMAN, J. Exper. Med. **46**:497, 1927.

The "sludge" phage of Clark and Clark did not cause any one of 102 human pathogenic streptococci. Erysipelas streptococci were "trained" to generate a lytic principle for strains of this group.

STUDIES ON A PARATYPHOID INFECTION IN GUINEA-PIGS: III. A SECOND TYPE OF SALMONELLA NATURALLY APPEARING IN THE ENDEMIC STAGE. JOHN B. NELSON, J. Exper. Med. **46**:541, 1927.

The spontaneous appearance of a second paratyphoid infection in a guinea-pig population during the endemic stage of an earlier epidemic is reported. A comparative study of the gross pathology of the two infections indicated a difference in the loci of development of the respective organisms in the animal host. The two types were readily differentiated by direct agglutination with specific immune serums. From its agglutinative affinities the second organism was judged to be an aertrycke type of *B. paratyphi.* AUTHOR'S SUMMARY.

VARIATIONS IN THE SCOURS TYPE OF BACILLUS COLI FROM THE STANDPOINT OF BACTERIOPHAGIC ACTION. JOHN B. NELSON, J. Exper. Med. **46**:549, 1927.

A lytic agent was not demonstrable in culture filtrates of either the parent or variant type of the scours organism. The parent type was resistant to the action of a "weak" bacteriophage, obtained from the animal host, while the variant type was susceptible. Exposure of the variant type to the scours bacteriophage was attended by agglutination of the cells, marked swelling, and an alteration of the contents prior to lysis. The manifestations of variation which regularly occur on agar plate cultures of the scours organism do not appear to be the result of bacteriophagic stimulation. AUTHOR'S SUMMARY.

MICROBIC VIRULENCE AND HOST SUSCEPTIBILITY IN PARATYPHOID-ENTERITIDIS INFECTION OF WHITE MICE: XII. THE EFFECT OF DIET ON HOST RESISTANCE; FURTHER STUDIES. IDA W. PRITCHETT, J. Exper. Med. **46**:557, 1927.

When 5 per cent of butter fat or cod liver oil is added to a bread and milk diet, in itself adequate to promote the breeding and rearing of a healthy stock of mice through a period of years, the resistance of these mice to per os infection with the paratyphoid mouse typhoid bacillus (*B. pestis-caviae*), as compared to that of mice on the unmodified diet, is definitely increased. A similar effect may be obtained with a McCollum "complete" diet, even when the butter fat is omitted, and with a bread and milk diet in which the milk used has been rayed with a mercury vapor lamp. When an inactive fat like Crisco is added to the bread and milk diet, the results obtained are not very clear-cut. While seasonal fluctuations in resistance to mouse typhoid were not completely eliminated by the various modified diets, they were nevertheless reduced, the modified diets tending to stabilize the death rate at a point lower than that usually reached by the mice on the control diet. AUTHOR'S SUMMARY.

ON THE NATURE OF THE "GOLGI BODIES" IN FIXED MATERIAL. C. E. WALKER and M. ALLEN, Proc. Roy Soc. **101B**:468, 1927.

"The Golgi elements and apparatus, and some of the structures described as chondriosomes in preparations treated with osmic acid, are probably artifacts produced by the methods used to demonstrate them. Hardy and others have shown that the ground substance of protoplasm, as seen in fixed preparations, may be reproduced by treating certain colloidal solutions in the same way as protoplasm. Golgi elements, bodies and apparatus do not appear in microscopic

preparations if acetic acid is a component of the fixative used. After fixation without acetic acid, they blacken when subjected to the action of osmic acid. If lecithin and kephalin are added to certain colloidal mixtures, and films or drops of the mixtures are fixed without the use of acetic acid, structures exactly like Golgi elements, bodies and apparatus are produced. These structures do not appear if acetic acid is used in the fixative. Lecithin and kephalin are broken up by acetic acid. Both are found in all cells. These artificial structures behave in the same way as the Golgi apparatus when treated with osmic acid, and when washed with turpentine. When a fine oleaginous emulsion is added to the colloidal mixtures, the structures produced by fixation and osmication appear to behave in a similar manner in relation to the globules of the emulsion as the Golgi elements to the nucleus of the cell." AUTHORS' SUMMARY.

ON THE IDENTIFICATION OF PATHOGENIC BACILLI OF THE INTESTINE. LOMRY and GILLET, Ann. de l'Inst. Pasteur **41**:648, 1927.

The differentiation of the gram-negative pathogenic bacilli of the intestine rests on sugar fermentation, agglutination, and absorption of agglutinins and finally on serologic study of the organisms in question. Repeated subculturing of a strain will often bring back its true diastase activity. G. B. RHODES.

IDENTITÉ ENTRE SPIROCHAÈTES ET BACILLES FUSIFORMES. LES HÉLICONÈMES "VINCENTI." G. SANARELLI, Ann. de l'Inst. Pasteur **41**:679, 1927.

The author succeeded in securing good growth of cecal spirochetes. A characteristic growth was secured in ordinary broth seeded also with *B. mesentericus-vulgatus*, due to the metabolic products of the latter. The culture acquires the morphology of the fusiform bacillus, but the change is not stable. Prolonged exposure to the air will, however, cause to be developed a fixed strain of the fusiform bacillus, which has lost wholly or in part its property of forming a helicoid, and may logically be called *"Heliconema vincenti."* The presence of fusiform types on the outside and of spirochetes in the deeper recesses of lesions may thus be explained.

Both types produce a quantity of spheroid bodies the rôle of which is questionable. Both act the same on animals, multiplying exceptionally or not at all, pathogenicity apparently being due to toxic proteins. On animal passage fusiform cultures tend to regain their power to curl. No gas or odor is produced in lesions. They are fragile, requiring partial anaerobic conditions. Two excellent plates of twelve figures each are given. The author considers his observations to be of general application where fusiform and spirochetal organisms are associated. MAX P. MARSHALL.

THE INVISIBLE AND FILTRABLE FORMS OF VISIBLE BACTERIA: III. PAUL HAUDUROY, J. de physiol. et de path. gén. **25**:523, 1927.

D'Herelle, Hauduroy and others have noted the appearance of "secondary" cultures in bacteriophage-lysed culture tubes. These are filtrable forms, differing greatly from the typical strains. Dysentery cultures, e. g., from a first filtration, fermented certain sugars without the production of gas, others with the production of gas; on a second filtration the production of gas was specifically reversed. Filtrable forms are noted in the typhoid and paratyphoid bacilli, the colon bacillus, the staphylococcus, the enterococcus, and the plague bacillus. Although difficult to isolate and bring to a recognizable form, this can be accomplished in many instances. Filtrable forms were found in water, and demonstrated in the stools of patients with typhoid. Filtrable forms of the *Eberth bacillus* were demonstrated to be present in the blood of a patient with typhoid fever.

M. S. MARSHALL.

THE INVISIBLE AND FILTRABLE FORMS OF VISIBLE BACTERIA: IV. PAUL HAUDUROY, J. de physiol. et de path. gén. **25**:537, 1927.

In a discussion of invisible filtrable forms of bacteria the author upholds the concept. Hypothetic correlation of bacteriophage action in vivo with the idea of filtrable forms is made. It is suggested that the reason the typhoid organism is not found in infected water may be the existence of infective filtrable forms. The longevity of the bacillus of dysentery in nature as a potential source of infection is contrasted with the relatively short life of this organism in the laboratory. It may be possible to explain the existence of bacterial species associated with filtrable viruses, as in hog cholera. The author is primarily concerned with demonstrating that it is logical to believe that invisible filtrable forms of bacteria may exist under certain circumstances, and with pointing out the usefulness of such a conception.

M. S. MARSHALL.

MORPHOLOGY OF PULMONARY FOCI IN GUINEA-PIGS CAUSED BY INTRATRACHEAL TUBERCULOUS INFECTION. W. PAGEL, Beitr. z. Klin. d. Tuberk. **66**:588, 1927.

The pulmonary foci which are produced by intratrachael infection show definite marks of differentiation from foci produced by inhalation. Large accumulations of leukocytes are frequently more predominant than caseation. These accumulations of leukocytes lead to a liquefaction of previously caseous tissue whose destruction can easily be followed. In this act, the leukocytes themselves undergo karyorrhexis. The general structure of these foci is more of the multilocular type than the inhalation foci. This is explained by the larger numbers of bacilli which are introduced into the bronchial tree. The smaller the number of infecting bacilli the more does the focus show a uniform and round structure.

MAX PINNER.

THE WHITE BLOOD PICTURE OF THE TUBERCULOUS GUINEA-PIG. J. BUCHHEIM, Beitr. z. Klin. d. Tuberk. **66**:599, 1927.

The blood picture of the tuberculous guinea-pig is characterized by neutrophilia and monocytosis. Both these alterations are intensified by chronic metal poisoning. Feeding of cholesterol does not influence the blood picture materially but leads to a slight decrease in monocytes. Both in metal poisoning and after cholesterol feeding the lymphopenia is more pronounced.

MAX PINNER.

THE INFLUENCE OF STARVATION AND OF STAPHYLOCOCCIC INFECTION ON TUBERCULOUS RABBITS. K. HENIUS, Beitr. z. Klin. d. Tuberk. **66**:616, 1927.

A small series of tuberculous rabbits were exposed to starvation and to infection with staphylococci. The influence of starvation is not much pronounced and slow. The superinfected animals died much sooner than the controls. The relation of these experimental observations with conditions in human beings is discussed.

MAX PINNER.

LINGUATULA LARVAE IN THE HUMAN LIVER. K. SONOBE, Virchows Arch. f. path. Anat. **263**:753, 1927.

Sonobe detected the larvae of *Linguatula rhinaria* in the liver in sixteen of 500 human necropsies in Berlin. The larvae were dead and encapsulated. This parasite is not considered to be of any pathologic significance in the human being.

O. T. SCHULTZ.

NEGRI-NEGATIVE RABIES. F. SCHWEINBURG, Virchows Arch. f. path. Anat. **265**:210, 1927.

The brains of 3,778 animals were examined for rabies in Vienna in the years 1919 to 1926; 2,041 were found negative for Negri bodies. Inoculation of

animals proved that 5.23 per cent of the brains that were negative for Negri bodies contained the virus of rabies, the percentages being especially high, 22.5 and 25, in cats and horses. Microscopic examination of tissue that did not contain Negri bodies and which yielded positive inoculations in animals showed the presence of the intracellular dustlike particles which had been described by Babes and J. Koch. The author considers these to be an early state of the rabies virus, but their demonstration is so difficult that they do not afford much practical aid in the microscopic diagnosis of rabies.

O. T. SCHULTZ.

THE SIGNIFICANCE OF VARIABILITY FOR THE TYPE DIFFERENTIATION OF THE PARATYPHOID B BACILLI. SAKUTAI TEY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:320, 1927.

The formation of a mucin coat is a variable factor among members of the paratyphoid B group, according to Tey, and is no safe differentiation between paratyphoid fever and food poisoning strains. He observed transformation from one type to another on four different occasions, twice from a type Freiburg to a type Breslau; twice from a type Freiburg to a type paratyphoid B.

PAUL R. CANNON.

TYPE DIFFERENTIATION OF THE PARATYPHOSUS B GROUP WITH FOWL AND SWINE IMMUNE SERUM. K. OIKAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:381, 1927.

Fowl immune serums for paratyphosus B bacilli differ from rabbit serums in that they contain agglutinins against food poisoning strains only. No differences were found with variants of the same original strain. Two swine immune serums, against a human type *B. paratyphosus* B and a food poisoning type (Breslau) showed no differences from rabbit serums to the same types.

PAUL R. CANNON.

RECEPTOR ANALYSIS OF BACILLUS ENTERITIDIS GÄRTNER. SAKUTAI TEY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:388, 1927.

Tey finds two types of Gärtner bacilli, one possessing both a coarse and fine flocculating receptor, the other only a fine flocculating one. He describes his observations in the comparison of these organisms with typhoid and paratyphoid strains.

PAUL R. CANNON.

THE ANTIBIOSIS BETWEEN THE PARATYPHOID B BACILLI AND BACILLUS COLI. SAKUTAI TEY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:401, 1927.

By symbiotic cultures, Tey finds that some *B. coli* strains are antagonistic to *B. paratyphosus* B while others have no such action. It is not possible to differentiate human from animal paratyphoid B strains by this method. Animal experiments attempting to show antagonistic relationship between *B. coli* and *B. paratyphosus* B were unsuccessful.

PAUL R. CANNON.

ALOPECIA IN EXPERIMENTAL RATBITE FEVER IN RABBITS. M. ABE, Acta Dermatol. (Japanese), Supplementary B2, 1927.

In about one third of 122 rabbits infected with ratbite fever loss of hair on the face and ears was observed with cell infiltration in the cutis, proliferation of fibroblasts and some superficial necrosis. After the lapse of from 44 to 198 days after the infection in about half of these rabbits the blood contained spirochetes at the beginning of the alopecia. Mercury, and especially arsphenamine, tended to cure the alopecia.

EXPERIMENTAL SYPHILIS IN NEW-BORN RABBITS. T. SHIMODA and M. HONDA, Acta Dermatol. (Japanese) **10**:61, 1927.

Newly born rabbits may be inoculated with the spirochete of syphilis either intravenously or subcutaneously in the genitals. Some of the animals injected intravenously developed syphilis of the nasal bones.

Immunology

OBSERVATIONS WITH THE PRECIPITIN REACTION. LUDVIG HEKTOEN, J. Immunol. **14**:1, 1927.

The serum proteins, hemoglobin and the specific precipitinogen in semen appear to be distinctive or specific for the species, and consequently presumably different chemically in each species, while the lens proteins, fibrinogen and thyroglobulin appear to be more or less closely related in many distinct species. Of this latter group, the lens and casein have been the standard illustrations to which we now can add fibrinogen and thyroglobulin. That fibrinogen should disregard so completely the species limitations of the immune reactions of serum and its constituents as well as of hemoglobin is both surprising and interesting. In fibrinogen the blood reveals a much wider antigenic relationship than is ordinarily assumed to be the case. It is of special interest in connection with the fundamental problems of immune specificness and the production of antibodies that these nonspecies-specific antigens can evoke the formation of corresponding antibodies in the homologous species, at least under certain conditions. In view of this circumstance may it not be well to subject to renewed experimental scrutiny the old assumption that species-specific antigens are incapable of provoking any antibody response in their own species?

AUTHOR'S SUMMARY.

SENSITIZATION OF TUBERCULOUS GUINEA-PIGS WITH EGGWHITE AND TIMOTHY POLLEN. L. DIENES and E. W. SCHOENHEIT, J. Immunol. **14**:9, 1927.

THE TRANSFER OF LOCAL HYPERSENSITIVENESS OF TUBERCULOUS GUINEA-PIGS WITH THE BLOOD SERUM. L. DIENES, ibid. **14**:43, 1927.

HYPERSENSITIVENESS OF GUINEA-PIGS TREATED WITH EGGWHITE DURING SMALLPOX VACCINATION. L. DIENES, ibid. **14**:53, 1927.

GENERAL CONSIDERATIONS OF LOCAL HYPERSENSITIVENESS. L. DIENES, ibid. **14**:61, 1927.

The results of this work confirm the observations of Lewis and Loomis that in tuberculous infection of the guinea-pig there is an increased antigenic response. Strong hypersensitiveness may develop. The connection between hypersensitiveness and antibodies in the serum remains undecided.

THE HETEROGENETIC HAPTENE. K. LANDSTEINER and P. A. LEVENE, J. Immunol. **14**:81, 1927.

In attempting to purify the specific part in alcohol extracts of the kidneys of the horse, fractions were obtained that differ from common lipoids in being soluble in water. The method of preparing this product is described. It is possible that the preparations contain specific groups similar to those in bacterial haptenes (Avery and Heidelberger).

EXPERIMENTAL IMMUNIZATION IN POLIOMYELITIS. W. LLOYD AYCOCK and J. R. KAGAN, J. Immunol. **14**:85, 1927.

It was found that attenuated virus was little less if not as pathogenic as active virus on subcutaneous injection in monkeys. The intracutaneous injec-

tion of active virus did not produce infection and appeared to protect monkeys from intracerebral injection of active virus to considerable degree. The blood serum of monkeys injected by the intracutaneous method neutralizes poliomyelitic virus in vitro. The results support the hope that immunity to epidemic poliomyelitis may be produced without active symptoms.

DISTRIBUTION OF IMMUNE AGGLUTININS IN THE SERUM AND ORGANS OF RABBITS. JULES FREUND, J. Immunol. **14**:101, 1927.

On passive immunizations agglutinins accumulate in the organs of rabbits, the rate of accumulation being greater in the liver, spleen, kidney and lungs than in the uterus and skin. After seventeen hours the agglutinins in the uterus and skin appear to become perfusion-fast. A similar accumulation of agglutinins takes place after the injection of killed *B. typhosus*.

THE CONTINUOUS INJECTION OF ANTIGEN IN SENSITIZED DOGS. WILLIAM F. PETERSEN and ERNST FRIEDRICH MÜLLER, J. Immunol. **14**:111, 1927.

On continuous injection of antigen into sensitized dogs, there follows in the lymph a succession of wavelike fluctuations in the carbon dioxide combining power, the K/Ca ratio, the lymph sugar, the leukocyte curve, etc. On recovery, the K/Ca ratio and the carbon dioxide combining power of the lymph may be higher than during the control period.

THE INTRADERMAL TEST FOR THE VIRULENCE OF DIPHTHERIA CULTURES. CHARLES S. GIBBS and CHEN KEN, J. Immunol. **14**:137, 1927.

The intracutaneous test for preliminary standardizing of diphtheria toxin and for determining the virulence of diphtheria cultures gave satisfactory results.

STUDIES IN ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS; A SIMPLE DIRECT METHOD OF STUDYING THE ABSORPTION OF UNDIGESTED PROTEIN. MATTHEW WALZER, J. Immunol. **14**:143, 1927.

By the intradermal injection of serum of persons hypersensitive to fish or egg, it is possible to sensitize a person passively and locally to these proteins. On taking such proteins into the stomach, under proper conditions, a wheal develops at the sensitized area indicating the prompt absorption into the circulation of protein materials. It seems that the absorption of such materials may be of normal occurrence.

THE PREPARATION AND PURIFICATION OF POLLEN EXTRACTS. GORDON A. ALLES and ROBERT W. LAMSON, J. Immunol. **14**:181, 1927.

At least one half of the nitrogen present in pollen extracts is contained by substances that are not immunologically important. The presence of whole protein is difficult to show even in concentrated unpurified pollen extracts, though undoubtedly present. Washing the pollen grains with 80 volume per cent of alcohol removes a considerable amount of inactive substances. This treatment, followed by the usual extraction of the active substances, yields extracts that are clinically somewhat less active than standard extracts.

AUTHORS' SUMMARY.

OBSERVATIONS ON IRREGULARITIES IN HUMAN ISOHEMAGGLUTININS. G. R. LACY, J. Immunol. **14**:189, 1927.

Four patients, acutely sick, are reported whose blood serums contained abnormal agglutinating substances for all four groups of human red corpuscles. One patient's blood contained auto-iso-agglutinins, while the other three did

not. Three of the patients had bacteremias due to encapsulated organisms. The disturbance of the iso-agglutinins was not constant, but in one case ran practically parallel with the temperature curve. Experimental evidence is offered to show that the disturbance of the iso-agglutinins was probably not due to a change in p_H of the blood nor to the hyperpyrexia per se. Other evidence is presented showing that there are members of the encapsulated, gram-negative group of bacteria, namely, certain strains of *B. acidi-lactici* and *B. lactis-aerogenes*, together with their products, which are capable of causing agglutination of human red corpuscles. Emphasis is here laid on the importance of invariably cross-testing the serum and the corpuscles of the donor and the recipient, before transfusion, even though they are members of the same iso-agglutinin group.

AUTHOR'S SUMMARY.

ANAPHYLACTIC CONTRACTION INDUCED THROUGH THE MUCOSA OF THE ISOLATED SURVIVING INTESTINE OF THE GUINEA-PIG. ARTHUR ISAAC KENDALL and PHILIP LEONARD VARNEY, J. Infect. Dis. **41**:156, 1927.

Anaphylactic contraction has been induced in isolated surviving strips of sensitized intestine of young guinea-pig by applying the homologous antigen to the mucosa.

These anaphylactic contractions have been relaxed with a dilute formaldehyde solution — when the formalin is added to the mucosa, and — when the formalin is added to the serous surface.

Evidence is presented which suggests that dilute sodium carbonate solution, creating an alkaline medium, aids the anaphylactic reaction.

The reaction induced in sensitized strips of intestine by the homologous protein, applied to the mucosa is suggestively similar to that induced by histamine under parallel conditions.

AUTHORS' SUMMARY.

THE POTENCY OF STORED PERTUSSIS VACCINES. LUCY MISHULOW, CAROLYN OLDENBUSCH and MARIE SCHOLL, J. Infect. Dis. **41**:169, 1927.

If the antigenic value of pertussis vaccines can be measured by their power to stimulate specific antibodies, and if the response in human beings is similar to that of rabbits to immunization with the vaccines, then properly stored vaccines remain antigenically potent for a considerable length of time, and the claim that pertussis vaccines lose about 75 per cent of their potency after storage for two or three months has not been substantiated. Eight different preparations, stored at from 8 to 10 C. and tested periodically, were highly potent at the end of four and one-half years.

AUTHORS' SUMMARY.

TISSUE HYDRATION AND ITS RELATION TO SUSCEPTIBILITY AND IMMUNITY: AS SHOWN BY SKIN TESTS IN ASTHMA, CHRONIC SINUSITIS AND OTHER INFECTIONS. WILLIAM B. WHERRY, J. Infect. Dis. **41**:177, 1927.

In addition to well recognized qualifications parasites must be capable of freeing water in the tissues. It is suggested that interaction between the parasite and the host leads to the production of amines in susceptible individuals and that the resulting hydration of the tissues favors the growth of the parasite.

Such interaction occurs when heat-killed bacteria are injected intradermally into human beings. The response varies with the species of bacteria and with the individual. The production of local urticaria, or this followed by immediate congestion is taken to indicate susceptibility; when the whole process is greatly aggravated the next day the reaction is taken to indicate sensitivity. Antigens so selected and given by the desensitization method yield excellent therapeutic results due to the production of opsonins and of a lessened tendency to tissue hydration.

AUTHOR'S SUMMARY.

AGGLUTININ RESPONSE TO CERTAIN BRUCELLA ABORTUS BACTERINS. S. J. SCHILLING and WM. L. BLEECKER, J. Infect. Dis. **41**:222, 1927.

Several types of *Br. abortus bacterins* and vaccines were tested for antigenic efficacy in rabbits. The results were determined by the agglutination titers of the rabbit serum at selected periods. From three separate trials the following points were determined.

Marked individual variations in antibody production in the treated animals were found. The data suggest that in many animals *Br. abortus* vaccine or bacterin will induce no immunity whatever.

The loss of antigenic qualities of *Br. abortus* cultivation on laboratory mediums was marked: a fact undoubtedly related to the variability of results already reported by investigators with large animals.

Treatment with live cultures did not uniformly induce a higher agglutination titer than treatment with bacterin. No uniform superiority appeared in any of the different types of bacterins in inducing high agglutination titer. The results do not indicate that the use of live cultures or of bacterins yields significant differences in the persistence of the immunity.

AUTHORS' SUMMARY.

THE KAHN TEST IN EXPERIMENTAL SYPHILIS. JOHN E. WALKER, J. Infect. Dis. **41**:233, 1927.

Based on a comparison of 400 presumably normal human serums and 29 presumably normal rabbit serums, a much higher incidence of positive Kahn reactions was obtained with the rabbit serums; 99.8 per cent of the human serums, and only 36 per cent of the rabbit serums were negative. The Kahn reaction with serums from rabbits increases in strength following their inoculation with syphilis. The strength of the reaction is usually in direct proportion to the clinical severity of the lesion.

The increase in the strength of the reaction is more marked and more prompt after intratesticular inoculation than after scrotal inoculation. With a decrease in the size of lesions the strength of the reaction decreases.

With reservations due to the limited number of animals studied, the Kahn reaction can be made specific for syphilis in rabbits by subtracting 40 quantitative units from the results.

In the one instance observed, the Kahn reaction fell to negative following treatment with neoarsphenamine. A clinical relapse was accompanied by a return of the reaction.

AUTHOR'S SUMMARY.

GAS PRODUCTION BY BACTERIAL SYMBIOSIS, WITH SPECIAL REFERENCE TO THE INFLUENCE OF NITROGENOUS SUBSTANCES. MITSUTERU ISHIKAWA, J. Infect. Dis. **41**:238, 1927.

The nonproteolytic, gas-forming bacteria alone cannot produce noticeable amounts of gas from carbohydrates and salts of formic acid in mediums containing only complex nitrogenous substances, as milk, ascitic fluid, casein, nutrose and gelatin, but gas is generated intensively by these bacteria in such mediums if they are grown in association with the proteolytic bacteria, and demonstrable amounts of gas are formed if simple forms of nitrogenous substances — the digestion products of proteins, peptone, amino-acids and ammonium salts — are added to such mediums.

The formation of gas from carbohydrates by the associative cultures of two kinds of saccharolytic bacteria, an acid-producing organism and a gas-forming bacterium, does not take place markedly in ascitic fluid, casein, nutrose and gelatin mediums, except under the following conditions: When a proteolytic organism is cultivated in association with the two saccharolytic bacteria; or when simple nitrogenous substances — peptone, amino-acids or ammonium salts — are added to the mediums.

The rôle played by the proteolytic bacteria in the foregoing cases is that they pave the way for the fermentative activity of the saccharolytic bacteria by breaking down the proteins of the mediums into simple forms of nitrogenous substances which apparently are essential to the formation of gas.

It is probable that such simple nitrogenous substances accelerate the activity or the production of the specific enzyme, formiase, which is thought to be responsible for the production of gas.

Many of the ammonium salts, as the sole source of nitrogen, satisfy the bacterial requirements for growth and for fermentative activity, but ammonium benzoate and ammonium salicylate are unsuitable for either of these requirements.

AUTHOR'S SUMMARY.

THE VALUE OF THE COMPLEMENT-FIXATION TEST IN THE DIAGNOSIS OF TUBERCULOSIS, WITH SPECIAL REFERENCE TO ITS RELATION TO THE TUBERCULIN SKIN REACTION. RAO BAHADUR M. KESAVA PAI and K. VENKATA RAU, Tubercle **8**:366, 1927.

The immune bodies concerned in the complement-fixation test and tuberculin reaction cannot be identical. While the complement-fixation reaction is due to the presence of immune body for the tubercle bacillus, the tuberculin reaction must be the effect of a different substance, an "antituberculin" which in combination with the test tuberculin produces the tuberculin reaction. This "antituberculin" is present in a comparatively large number of clinically nontuberculous cases.

H. J. CORPER.

PATHOGENETIC AND ANATOMIC RELATIONS BETWEEN DEATH FROM BURNS AND ANAPHYLACTIC CRISIS. G. ANDREI, Arch. per le sc. med. **49**:44, 1927.

Andrei was unable to observe any clinical or anatomic signs resembling anaphylactic shock in guinea-pigs subjected to experimental burns. He believes that the changes described by Brancati — especially the white nodules consisting of a granular mass surrounded by lymphocytes and histocytes were manifestations of pseudotuberculosis rodentium.

K. SCHULHOF.

ANAPHYLACTIC SHOCK, PEPTONE SHOCK AND CURARIZATION. B. POLETTINI, Arch. per le sc. med. **49**:129, 1927.

Contrary to C. Foà's observations, curare did not prevent the peptone shock in the author's experiments on dogs. It also proved ineffective in prevention of anaphylactic shock in rabbits and dogs.

K. SCHULHOF.

BLOOD GROUPING IN TUBERCULOSIS. B. KALLABIS, Beitr. z. Klin. d. Tuberk. **66**:391, 1927.

One thousand and seventy patients were grouped; 515 of them had active pulmonary tuberculosis, 555 had no signs of active tuberculosis. It was found that the group "A" seems to have a somewhat greater, and group "O" a somewhat lesser tendency to tuberculosis.

MAX PINNER.

EXPERIENCES WITH THE TUBERCULOSIS REACTION ACCORDING TO WASSERMANN. E. BÖRNER, Beitr. z. Klin. d. Tuberk. **66**:405, 1927.

A further series of 787 patients was examined. The results were as follows: 11 per cent positive reactions were found in nontuberculous patients, 72 to 81 per cent positive reactions in active tuberculous patients, and 27 per cent positive in inactive tuberculosis. The reaction is considered to be sufficiently specific to aid materially in the diagnosis of tuberculosis under consideration of all the clinical observations.

MAX PINNER.

EXPERIENCES WITH THE TUBERCULOSIS REACTION ACCORDING TO NEUBERG-KLOPSTOCK AND LEHMANN-FACIUS-LOESCHKE. I. BUDDE, Beitr. z. Klin. d. Tuberk. **66**:562, 1927.

The first reaction demonstrates the presence of an antibody, or a complex of antibodies, which is particularly frequent in active tuberculosis. It is, however, not present in every patient with active disease. Cross fixations with Wassermann-positive serums occur. Positive reactions are obtained with the serums of nontuberculous patients although usually in weak degrees. The second reaction, which is a precipitation reaction with an extract from tuberculous tissues, is positive only in a limited percentage of tuberculous patients. It appears, however, to be specific to a high degree. Using both reactions simultaneously valuable diagnostic aids may be obtained.

MAX PINNER.

CHOLESTEROL DETERMINATIONS IN THE BLOOD OF PULMONARY PATIENTS. M. v. BABARCZY, Beitr. z. Klin. d. Tuberk. **66**:568, 1927.

On the basis of examinations on forty-one patients the following conclusions are drawn. In pulmonary tuberculosis the cholesterol content of the blood may be normal, increased or decreased. When the tuberculin allergy was artificially increased, the cholesterol content was usually decreased. In different patients with the same amount of allergy the cholesterol content is not necessarily the same. It is believed that the exudative, or the proliferative, character of the disease influences the cholesterol content. The material examined did, however, not permit a definite conclusion in this regard.

MAX PINNER.

SERUM DIAGNOSIS OF TUBERCULOSIS BY COMPLEMENT FIXATION ACCORDING TO BESREDKA, MATÉFY'S REACTION AND SEDIMENTATION RATE. W. HILGERS and G. HERHOLZ, Beitr. z. Klin. d. Tuberk. **66**:573, 1927.

In eighty-nine patients the tests were made at monthly intervals. It was hoped that the regular performance of these tests and the plotting of their results in the form of curves would furnish important diagnostic and prognostic data. The complement fixation was permanently positive only in 40 per cent of clinically definite tuberculosis. The sedimentation rate was increased permanently in 47 per cent. All three reactions gave fluctuating values which did not show any consistency comparing the three tests and comparing each test with the clinical course.

MAX PINNER.

THE DIFFERENTIATION OF HUMAN AND BOVINE BACILLI BY COMPLEMENT FIXATION. O. KIRCHNER, Beitr. z. Klin. d. Tuberk. **66**:584, 1927.

Human and bovine tubercle bacilli cannot be differentiated by complement fixation, using as antigens bacillary suspensions and as serums artificial immune serums against the bacillary strains tested.

MAX PINNER.

EXPERIMENTAL PRODUCTION OF COMPLEMENT-FIXING ANTIBODIES AGAINST FAT SUBSTANCES OF SIMPLE CONSTITUTION. J. E. WOLF, Beitr. z. Klin. d. Tuberk. **66**:710, 1927.

Relatively simple fats, such as human fat, can stimulate the production of specific antibodies when injected with proteins such as bacterial protein, pig's serum and the protein of certain apathogenic micro-organisms.

MAX PINNER.

OBSERVATIONS OF BIRD POX. T. SAITO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:100, 1927.

Saito describes further details of the immunologic reactions in bird pox.

PAUL R. CANNON.

THE PRESENCE OF NORMAL HETEROPHIL HEMOLYSIN IN ANIMALS OF THE GUINEA-PIG AND RABBIT TYPE. P. L. RUBINSTEIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:114, 1927.

Rubinstein discusses the question of heterophile antibodies and antigens in various animals and concludes that Friedemann's theory is incorrect.

PAUL R. CANNON.

AN AGGLUTININ ANALYSIS OF BACILLI OF THE PARATYPHOID B, HOG CHOLERA AND PARATYPHOID A GROUPS. K. AOKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:126, 1927.

Aoki divides the groups into four types, viz., paratyphoid B. schottmülleri, mouse typhoid, hog cholera and paratyphoid A. Furthermore, they are of two forms, specific and nonspecific, according to their agglutination reactions. His methods of determining these two forms and the significance, are given.

PAUL R. CANNON.

THE RECEPTOR ANALYSIS OF THE PARATYPHOID B GROUP (SCHOTTMÜLLER). K. OIKAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:212, 1927.

The use of the receptor analysis of the paratyphoid B group shows three types: a food poisoning, type Breslau, which possesses only one receptor; a food poisoning type Freiburg which has two receptors and a human type paratyphoid B which has the above receptors plus a third. He also found several sources of error in the use of Castellani's absorption tests.

PAUL R. CANNON.

SEROLOGIC CHANGES IN PARATYPHOID B BACILLI AS INFLUENCED BY GROWTH WITH IMMUNE SERUM. Y. SHIIBA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:278, 1927.

The growth of various strains of the paratyphoid B group in broth with type specific serums did not lead to any serologic variations, even after some weeks of such treatment.

PAUL R. CANNON.

THE RÔLE OF THE ECTO- AND ENDOPLASM OF TYPHOID BACILLI IN IMMUNE REACTIONS. K. HOFMEIER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:509, 1927.

Hofmeier states that the presence of endoplasmic antibodies is necessary for a bactericidal action against typhoid bacilli. In the phagocytosis of typhoid bacilli both ectoplasm and endoplasm antibodies are of significance, although here, too, the endoplasm antibodies are more effective.

PAUL R. CANNON.

THE BACTERICIDAL ACTION OF BLOOD AND SERUM AGAINST STAPHYLOCOCCI. L. K. WOLFF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **50**:543, 1927.

Wolff has demonstrated that the intravenous injection of killed staphylococci or the rubbing into the skin of living cultures, causes the appearance of bactericidal properties in the blood of rabbits. These bactericidal substances are specific and originate through the leukocytes which kill the bacteria, but not through phagocytosis. The employment of antistaphylococcic serum did not cause any favorable influence on the bactericidal action, either in vivo or in vitro.

PAUL R. CANNON.

Tumors

FURTHER OBSERVATIONS ON THE INABILITY TO TRANSMIT A RABBIT NEOPLASM BY CELL-FREE MATERIALS. LOUISE PEARCE and JAMES B. MURPHY, J. Exper. Med. **46**:205, 1927.

It has not been possible to propagate a malignant neoplasm of the rabbit with cell-free filtrates, or desiccated tumor tissue or by the use of fluid mediums kept in contact with tumor tissue. These observations confirm the results of previous experiments carried out with early generations of the tumor. The existence of an agent distinct from the tumor cell which could initiate growth has not been demonstrated. The experiments bring out an essential biologic difference between this mammalian neoplasm which is considered to be of epithelial origin and certain filtrable tumors of fowls which have been classified as sarcomas.

AUTHORS' SUMMARY.

THE METABOLISM OF TUMORS IN THE BODY. O. WARBURG, F. WIND and E. NEGELEIN, J. General Physiol. **8**:519, 1927.

Using transplanted tumors of Flexner-Jobling's rat carcinoma or of Jensen's rat sarcoma, it was found possible to maintain detached portions in living condition for considerable periods of time in conditions which deprived the tissues of the function of oxidation or of fermentation, but not of both simultaneously. Having this double source of energy, it would appear a difficult matter to kill tumor cells within the living body by want of energy, were it not for the fact as estimated by consumption of dextrose, that tumors appeared to have a far less adequate supply of this than normal tissues. The consumption of dextrose by tumor cells was found to be two-thirds by fermentation and one-third by oxidation. The fermentative process was easily affected by changes in concentration of dextrose, so much so that the fermentation normally achieved by an entire tumor of sufficient size is only one half of the possible maximum. That this low value was the result of an insufficient supply of dextrose reaching the more remote parts of the tumor was shown by increasing the dextrose content of the afferent blood to the point where it provided optimum concentration in the venous blood from the tumor, when practically the maximum of fermentation occurred. But in living animals deprivation of dextrose alone was without effect on the tumor, as was shown by keeping animals with tumor at low blood sugar content for hours, by means of insulin administered at the convulsive stage, without appreciable effect on the activities of the tumor tissue, as afterward measured. A much more pronounced effect was obtained by deprivation of oxygen, rats with tumor being kept in an atmosphere of 5 volume per cent of oxygen for several hours, a small amount of ammonia being present to prevent acidosis. Theoretically, it was anticipated that the venous half of the tumor would be killed in this way,—because of the poor natural provision of dextrose in this part of the tumor, and the added deficiency of oxygen here. Practically the entire tumor except for a thin outer shell was killed in this way. The authors explain this by destruction not only of the distal part of the tumor, but of the capillaries here as well, with resultant vascular occlusion sufficient to destroy most of the remainder of the tumor.

H. E. EGGERS.

ON TAR CANCER OF THE SEMINAL VESICLES. P. L. BADILE, Tumori **1**:1, 1927.

Badile injected approximately 0.5 cc. of tar into the seminal vesicles of ten white rats. Three died prematurely with parenchymatous degeneration of the internal viscera, especially of the kidneys; six died of bronchopneumonia from one to eleven months after the operation. The one that survived longest succumbed to a pyelonephritis after one year. In five of the seven rats that remained alive a sufficient length of time, a metaplasia of the epithelium of the seminal vesicles into stratified squamous epithelium took place. The rat

that survived longest showed a typical malignant epithelioma with invasion of the surrounding structures and local metastases. The author believes that the initial change of the process is a hyperplastic proliferation of the epithelium followed by metaplasia. This metaplasia represents a precancerous stage. The action of the tar is evidently a local and not a general one. The general effect of the injections of tar is due to the easily absorbable parts of it while the remaining poorly absorbable rest produces the local changes. Locally, the tar is taken up by the cells in the form of minute droplets which in the cells undergo a physicochemical transformation and show an elective biochemical affinity for the nuclei. The inflammatory reaction in the surroundings of the carcinoma is not due to the development of the malignant tumor, but is caused by the agent which produces the carcinoma. The primary effect of the tar on the epithelium of the seminal vesicles is a necrotizing one just as on the cells in the rest of the body. Later the insoluble particles of tar as such or after they have undergone a physicochemical change in the cells excite the hyperplasia of the remaining epithelial cells with flattening and cornification of the superficial cell layers. The author has received the impression that the tar has the cancer producing action in so far as it contains the minute granules which on account of their biologic affinity are taken up by the nuclei.

W. Ophüls.

The Influence of Colloidal Sulphur on the Evolution of Experimental Tumors in White Rats. Luigi Zagni, Tumori **1**:42, 1927.

The colloidal sulphur arrests the development of experimental tumors of white rats and causes the tumors which have already been produced to disappear. The disappearance is preceded by a softening followed by a progressive diminution in size. The tumor cells are replaced by an inflammatory proliferation with regeneration of the layers of the cutis. The colloidal sulphur produces this effect in smaller doses than any other substance so far experimented with.

W. Ophüls.

On the Significance of Local Eosinophilia in Malignant Tumors. F. Battaglia, Tumori **1**:191, 1927.

Battaglia comes to the conclusion that the local eosinophilia in malignant tumors of man—not constantly but frequently in carcinoma, more rarely in sarcoma—is connected with a positively chemotactic substance which is elaborated by the tumor itself. His researches on dogs prove that lactic acid, when injected into the tissues in contradistinction to other substances, produces just such a reaction. He states that the hypothesis that the eosinophilia in malignant tumors is caused by the production of lactic acid by the tumor cells seems to be confirmed by the fact that lactic acid is produced in some malignant tumors of man in notable quantity and in others in small quantity with a certain correspondence between the results of the microscopic and of the biochemical investigation.

W. Ophüls.

Insulin in Tumor Tissue. A. H. Roffo and L. M. Correa, Ztschr. f. Krebsforsch. **24**:489, 1927.

Extraction of a transplantable spindle cell sarcoma of the rat yielded a substance whose blood sugar reducing effect equaled that of insulin. Because similarly acting substances can be obtained from many kinds of normal animal tissues, the presence of an insulin-like material in tumor tissue may simply be the result of accumulation of pancreatic insulin. That the material is a specific product of the tumor tissue, as is the case with certain plant tissues, is possible but is not susceptible to proof.

O. T. Schultz.

CHRONIC INFLAMMATION AND ATYPICAL EPITHELIAL PROLIFERATION. W. G. GARSCHIN, Ztschr. f. Krebsforsch. **24**:492, 1927.

Garschin attempted to study experimentally the effect of chronic inflammation on the causation of atypical epithelial proliferation by inducing granulomatous lesions of the subcutaneous tissue of rabbits by means of purified siliceous earth. A typical proliferation of the intact overlying skin did not occur, but when an area of skin over the inflammatory granuloma was excised, simulating a chronic ulcer, the reparative proliferation at the margin of the area became atypical and invaded the granulation tissue. If the underlying tissue had already become fibrous at the time of excision of skin, atypical proliferation did not occur. Whether the atypical proliferation was the result of physical, chemical or physicochemical factors exercised by the granulation tissue the author was not able to determine from his morphologic study.

O. T. SCHULTZ.

PYOGENIC ACTION OF INOCULATED TUMOR TISSUE. J. v. DARÁNYI, Ztschr. f. Krebsforsch. **24**:512, 1927.

When tissue from rapidly growing human carcinomas was introduced into a subcutaneous pocket of rabbits, an abscess resulted. Normal human tissue similarly introduced did not have this effect, nor did emulsions of tumor tissue injected subcutaneously. Tumor tissue obtained at necropsy did not have a pyogenic action, nor did fresh tumor tissue which had been kept in acriflavine, indicating that the pyogenic action is an effect of living tumor cells. The author concludes that living tumor tissue has a pyogenic action on a heterologous host, and that the absence of such action in the original host must be due to the presence in the latter of substances which protect against the pus producing action of the tumor cells. Bacteriologic controls are not recorded.

O. T. SCHULTZ.

HETEROTRANSPLANTATION OF MALIGNANT TUMORS. G. ROSKIN, Ztschr. f. Krebsforsch. **24**:515, 1927.

In a previous communication Roskin had reported the successful transfer of the Rous chicken sarcoma to white mice whose reticulo-endothelial system had been blockaded with saccharated iron oxide. He now reports the transfer of a spontaneous mammary carcinoma of a mouse and of a human mammary carcinoma to chickens after blockading of the reticulo-endothelial system. The resulting growths were alike and they had no morphologic similarity to the transplanted tumors, being composed of lymphoid cells. The author leaves unanswered the question, which he himself asks, as to whether the growth in the chickens was a lymphosarcoma or an inflammatory lymphogranuloma.

O. T. SCHULTZ.

THE EFFECT OF INCREASED OXYGEN TENSION ON CARCINOMA. A. FISCHER, E. B. ANDERSEN, F. DEMUTH and H. LASER, Ztschr. f. Krebsforsch. **24**:528, 1927.

Fischer and Andersen had shown in 1926 that normal tissues in vitro are more resistant to an increase in partial oxygen pressure than a transplantable carcinoma of the mouse. The present authors report the results of an attempt to apply this observation to the therapeutic treatment of mouse carcinoma in the living animal. They state that they have never seen spontaneous regression in 1,018 successful transplantations of the tumor used by them. The present work was based on 756 animals, of which 205 were controls. The experimental animals were subjected to a partial oxgen pressure of 1.6 atmospheres for twenty to twenty-two hours, or 2 atmospheres for fourteen hours. At higher pressures the animals died in convulsions; with the pressure used many of the mice developed pneumonia. In some of the experiments the animals also received subcutaneous injections of various copper or selenium combinations. With

increased oxygen alone the authors record 2 per cent as cured and 3 per cent as improved; with the addition of copper and other preparations the number cured reached 4 per cent and the number improved from 16 to 19 per cent. The procedures used caused widespread necrosis of the tumor tissue.

O. T. SCHULTZ.

IMMUNITY TO CHICKEN SARCOMA. A. FISCHER, Ztschr. f. Krebsforsch. **24**:580, 1927.

Fischer studied the immunity reactions against the Rous chicken sarcoma by means of the tissue culture method. Two factors enter into the successful inoculation of this tumor, the viable tumor cells and the filterable virus which is able to initiate growth in the absence of transplanted cells. One per cent of normal chickens were found to be refractory to both cells and virus, i. e., they were absolutely immune, and 40 per cent were found to be refractory to the virus alone, i. e., relatively immune. Chicken sarcoma cells could be grown for long periods of time in the presence of naturally immune chicken plasma, of normal heterologous duck and goose plasma, and of the plasma of actively immunized ducks, geese and rabbits with no loss of their ability to produce tumors when transplanted. The immune serum of the three heterologous species of animals and of absolutely immune chickens had the property of neutralizing the virus. This humoral factor is not effective against the virus within living cells. Since 40 per cent of normal chickens have a principle in their blood that is antagonistic to the virus, but only 1 per cent are immune to living cells, the growth of a tumor in an animal whose serum possesses the virus-antagonistic principle proves that such tumors are due to the multiplication of the transplanted cells. The animal which is absolutely immune has both a humoral principle antagonistic to the virus and an anticellular principle antagonistic to the living cells. The metastases of chicken sarcoma are held to be the result in most instances of the transportation, not of living cells, but of the virus alone. By determination of the absence or presence of the humoral principle, it is possible to predict in advance whether or not a successfully transplanted chicken sarcoma will metastasize.

O. T. SCHULTZ.

Medicolegal Pathology

TWO CASES OF DEATH FOLLOWING INSUFFLATION OF THE FALLOPIAN TUBES. G. L. MOERSCH, J. A. M. A. **89**:522 (Aug. 13) 1927.

In one case death is ascribed to air embolism from insufflation of the fallopian tubes. The tubes were found to be closed, and the uterus was then curetted during which the patient died suddenly. A few hours after death numerous gas bubbles were found in the right side of the heart, the inferior vena cava and the right femoral vein. The right fallopian tube contained blood and gas. In the second case sudden death followed tubal insufflation of oxygen at a pressure of nearly 200 mm. of mercury, but necropsy was not performed until after the body had been embalmed.

REPORT OF THE CHIEF MEDICAL EXAMINER OF THE CITY OF NEW YORK, 1925-1926. CHARLES NORRIS, M.D., Chief Medical Examiner.

This report of the outstanding agency in this country for the investigation of violent and accidental deaths is entirely statistical. Statistical tables do not readily lend themselves to further condensation, but attention may be called to some of the more significant figures. The total number of deaths in New York City (Greater New York) in 1925 was 71,864, the number of deaths investigated by the medical examiner's office was 13,353, the number of investigated cases filed with the district attorney was 4,062, and the number of postmortem examinations made by the office was 2,919. In other words, investigation by the medical examiner was deemed necessary in 18 per cent

of all deaths, 30 per cent of the deaths investigated required the attention of the district attorney, 5 per cent of all deaths in New York were subjected to necropsy by the medical examiner, and in 21 per cent of the deaths investigated, necropsy was performed. The value of the proper utilization of this volume of material for forensic medicine, for vital statistics and for pathology cannot be estimated. Other tables relate to the classification of the deaths investigated; 20,775 chemical examinations were made; these ranged from 3 examinations of pills, through 27 examinations of whisky and 47 identifications of human blood stains, to 1,142 examinations for wood alcohol and 8,952 for grain alcohol. The entire volume of work of the medical examiner's office was done at a total cost of $135,830.20. O. T. SCHULTZ.

MANOILOFF REACTION FOR DETERMINATION OF SEX. W. SACHS, J. M. A. S. Africa **1**:168, 1927.

This test is not of any value from a medicolegal point of view, because it is inconsistent.

SALIVA TEST ("DOCIMASIA SIALICA") IN NEW-BORN. V. M. PALMIERI, Arch. di antrop. crim. **47**:215, 1927.

Palmieri was unable to confirm any one of the statements made by S. Diniz in suggesting this new test of extra-uterine life. Diniz claimed that the newborn child swallows saliva which may be demonstrated in the stomach even in putrefaction. He suggested making tests for rhodanid, ptyalin and a specific protein of the saliva (precipitin test and anaphylaxis). Palmieri used these methods (except anaphylaxis) in forty-three fetuses, twenty-two of whom had been breathing. The results were — with one doubtful exception — negative. Besides this, if the results had been different, their value would be doubtful, since the fetus probably swallows even in the uterus. K. SCHULHOF.

DIAGNOSIS OF BLOOD BY ISO-AGGLUTINATION. VITTORIA SIRACUSA, Arch. di antrop. crim. **47**:307, 1927.

In a murder case, the blood spots on the clothes of the suspected person were shown by iso-agglutinative tests to correspond to the blood group of the suspect and not to the groups of the victims. In testing blood spots for iso-agglutinative elements, the tests would better be directed toward the agglutinogen rather than the agglutinins, particularly because the agglutinins disappear sooner and sometimes unevenly. The agglutinogen is demonstrated by its absorption of the corresponding agglutinin which is set free again on warming the mixture at 45 C.

XANTHOPROTEIN REACTION IN BLOOD IN MERCURIC CHLORIDE POISONING. M. AJAZZI-MANCINI, Arch. per le Sc. Med. **49**:119, 1927.

Becher's technic of estimation of the aromatic compounds in the filtrate of the serum (after precipitation of the proteins) was used in four cases of acute poisoning with mercuric chloride. This test gave a more faithful index of the gravity of the condition than the determination of residual nitrogen, urea and indican as made by the author. K. SCHULHOF.

BISMUTH POISONING. J. MUNCK, Dermat. Wchnschr. **84**:367, 1927.

Within eleven months a man, aged 45, received 5.13 Gm. of metallic bismuth in the course of treatment for syphilis. The first symptoms of poisoning were icterus and stomatitis; then the temperature became subnormal and delirium set in. Death occurred twelve days after the onset. In the meantime a dark line at the margins of the gums developed. Large amounts of bismuth were found in the internal organs, especially in the liver. Nephrosis, colitis and fatty changes in the liver and myocardium were present.

DEVELOPMENT OF GAS GANGRENE AFTER INJECTIONS OF MEDICAMENTS. R. WANKE, Deutsche Ztschr. f. Chir. **199**:214, 1926.

Twenty-five instances are collected. It is suggested that in most such cases the gas bacilli come from the cannula used in making the injection. Intramuscular injections in conditions of lowered vitality demand special precautions.

INJURY TO SKULL FROM ELECTRIC CURRENT. E. RANZI and OTHERS, Deutsche Ztschr. f. Chir. **200**:36, 1927.

A man was injured by an electric current while at work in an electric locomotive. The current entered the body above the right ear and passed out at the vertex, a little to the left. He was removed unconscious, but had recovered consciousness at the end of seven hours. The wounds were treated conservatively. In each the skin necrosis progressed and the bone became exposed. A month after the injury, epileptic attacks set in, with general paralysis of the right side of the face and the right upper extremity. Four operations were performed, at which epidural, subdural and abscesses of the brain were opened and the diseased bone cleaned away. Streptococci and pneumococci were found in the pus from the abscesses in the brain. The patient died two months after the injury. On microscopic examination the bone showed rarefying, sequestrating osteomyelitis, the necrosis limited by granulating inflammation. It is assumed that the electric current killed bone cells, which thus became a fit field for infection by extension from the suppurating soft parts.

THE IMPORTANCE OF DEGENERATION IN DETERMINING THE CAUSE OF PREMATURE DEATH. A. S. KRUJUKOV, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:444, 1926.

This is from an address by Krujukov at the eleventh national Russian Convention for Legal Medicine. He urged, from his thirty years experience with medicolegal postmortem examinations, that more attention be given to such "stigmas of degeneration" as irregularities of shape, thickness and compactness of the cranial bones, evidence of compression of the brain, including the amount of ventricular fluid, hypotrophy of the heart, aorta and other blood vessels and status thymicolymphaticus. He insisted that deaths from infections and from violence occur more easily when such conditions are already present. He also has frequently found them, as have others, in the bodies of persons who commit suicide.

E. R. LE COUNT.

VISCERAL INJURIES DUE TO JUMPING OR FALLING FROM HIGH PLACES INTO WATER. H. MERKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:517, 1926.

Jumping from high bridges into water they span is a favorite mode of suicide in many large cities. From such a bridge about 105 feet above the water in Munich, there were 106 attempts to commit suicide during twenty years ending with 1919; most of them were successful. Merkel reports what was found in three bodies by way of illustration, with a good summary of the impressions others have obtained from examining the bodies of persons killed in a similar manner. From impact with water solely, bones are rarely broken, but tears of the liver, spleen, lungs, kidneys and heart occur. In one body an extensive fat embolism in the lungs was encountered.

E. R. LE COUNT.

HEMORRHAGE INTO THE LUNGS OF NEW-BORN INFANTS. K. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:523, 1926.

From a careful gross and microscopic study of the hemorrhages in the lungs of 245 maturely or prematurely born infants dying during or soon after birth, not much that is new is suggested to explain their origin. They are practically

constant with premature birth and attributed to the greater ease with which the lungs may be torn by pressure in the birth passage at such periods of incomplete development and lesser ability to resist external violence. The subpleural ecchymoses are often found continued into the lung tissue as broad bands of hemorrhage in septums and about blood vessels. The blood is well absorbed at the end of the second or third week after birth, but frequently the regions of hemorrhage are infected and then more bleeding occurs. Infarcts are simulated.

Only subpleural hemorrhages were found in one of two infants suffocated after birth at term, there were no hemorrhages in the lungs of the other. With death from natural causes taking place slowly as it frequently does in infections, the lesser cardiac force causes both stasis and hemorrhage. The hemolysis accompanying putrefaction prevents recognition of hemorrhages in decomposed bodies.

E. R. Le Count.

Changes of the Endometrium Caused by Silkworm Gut Used to Prevent Conception. W. H. Stefko and A. Laurié, Deutsche Ztschr. f. d. ges. gerichtl. Med. **8**:536, 1926.

Interest having recently been drawn to intra-uterine contraceptive methods, particularly the use of silkworm gut, the authors introduced this into the uterus in two rabbits. The animals were then paired, killed after one month, and the entire genital tract examined microscopically. Evidence of pregnancy was not found. The endometrium was hyperemic and hyperplastic, the muscles edematous, the glands hyperplastic and a basophilic substance filled their channels. There was no other change. In material obtained by curettage from the uterus in two women, in which silkworm gut had been lodged one month, the same structural alterations were present. Similar changes with definitely loosened chorionic cells, an irregular, incompletely developed syncytium with necrotic areas were associated with two abortions after one and one-half months of pregnancy and four months after insertion of the silkworm gut.

The results are interpreted on a physiochemical basis, the suture material causing a transformation of glandular activity, a change in osmotic pressure and surface tension. It is known that after the introduction of silkworm gut, the uterine secretion becomes more alkaline. Normally it is from 7.5 to 8.0 p_H, and after silkworm gut is introduced, it changes to 9 or 9.4 p_H. This increased alkalinity arrests the activity of spermatozoa.

Louisa Bacon.

Accidents from Electricity. J. Fog, Ugesk. f. Laeger. **89**:339, 1927.

Fog describes four cases of death or supposed death from electric shock and reviews at the same time Jellinek's book on "Der elektrische Unfall." In one of the cases reported typical electric marks were found on the upper part of the back, the left hand and right foot corresponding to the places in which the current entered and passed out of the body. In another case a similar mark on the left thumb corresponding to the entrance of the current. These marks were characteristic in that the adjacent hairs were intact without signs of having been burned. In the first case the clothes and shoes of the victim presented typical perforations corresponding to the lesions on the back and on the right foot. It is pointed out that it is always of great importance to examine carefully the clothes and shoes of the victims of electric shock. In the two cases mentioned the internal examination showed cerebral and pulmonary hyperemia which is interpreted to mean that death did not occur immediately. It is mentioned also that in all cases of apparent death from electric shock prolonged efforts at resuscitation by artificial respiration are indicated. The efforts should be continued for three or four hours. Physicians are slow to learn that death from electricity may be only apparent, and that prolonged and energetic efforts at resuscitation are demanded.

ATTEMPT AT SUICIDE WITH INSULIN. K. SECHER, Ugesk. f. Laeger. **89**:378, 1927.

A patient, aged 28, with diabetes of long standing, took a single massive dose of 60 units of insulin with suicidal intent during an attack of depression. Immediately he regretted what he had done and took two tablespoonfuls of sugar; he recovered. Secher suggests the possibility of murder being committed with this substance, in which case the cause of death would be difficult to prove at necropsy.

AGGLUTINATION REACTION FOR DETERMINATION OF BLOOD GROUPS. G. ALIEFF, Russkaya Klinika **7**:55, 1927.

The author presents a method of identifying blood stains as to group. It is based on the property of erythrocytes of absorbing agglutinins. This property is retained by the agglutinogens in the erythrocytes of dried blood for at least eight weeks. The method is as follows: 1 Gm. or less of the dried blood to be examined is mixed with 1 cc. of serum of group O. The mixture is kept in the thermostat at 37 C. for from two to five minutes. The mixture is then tested against corpuscles of groups A and B. The results are read as follows: if the mixture does not agglutinate the cells of A or B, the dried blood belongs to group AB; if the mixture agglutinates corpuscles of A but not of B, the dried blood belongs to group B; if the mixture agglutinates corpuscles of B but not of A, the dry blood belongs to group A; and if the mixture agglutinates the corpuscles of both A and B, the blood stain belongs to group O. The medicolegal applications of the test are discussed.

LAURENCE H. SNYDER.

Technical

A MICRO METHOD FOR THE QUANTITATIVE DETERMINATION OF CARBON DIOXIDE IN BLOOD AND OTHER SOLUTIONS, AND SOME OBSERVATIONS ON THE EFFICIENCY OF PARAFFIN OIL AS A MEANS OF KEEPING CARBON DIOXIDE IN SOLUTION. D. RAFFEL, J. Biol. Chem. **74**:839, 1927.

A method is described for the determination of small amounts of carbon dioxide in the blood and other solutions. It is accurate for amounts between 0.1 and 0.5 cc. of carbon dioxide, with an error not exceeding 1.1 per cent by volume. The method is based on the absorption of carbon dioxide in a standard barium hydroxide solution, with subsequent titration. By the aid of this method it was found that normal serum kept under liquid petrolatum loses only 2 per cent or less of its carbon dioxide in the course of twenty-four hours. However, when large quantities of carbon dioxide are present the loss may amount to 10 per cent of the carbon dioxide contained in the serum.

AUTHORS' SUMMARY.

STUDIES ON URINARY ACIDITY, AND A METHOD FOR ELECTROMETRIC TITRATION OF URINE. S. MORGULIUS and W. R. HAMSA, J. Biol. Chem. **74**:851, 1927.

A simple method is described suitable for titrating electrometrically to a desired p_H in the presence of quinhydrone. Urine is titrated to a p_H 7.40, the average reaction of the blood, a buffer mixture of the same p_H and the titrated urine forming each a half cell, connected by means of an agar potassium chloride bridge. The endpoint of the reaction is registered by the zero deflection of the galvanometer. The significance of the urinary acidity and of the urine buffer value is discussed.

AUTHORS' SUMMARY.

THE MICROSCOPIC DEMONSTRATION OF STAINED TUBERCLE BACILLI IN THE LIGHT-DARK FIELD. M. J. GUTMANN, Beitr. z. Klin. d. tuberk. **66**:308, 1927.

With the method indicated in the title, which requires a special light dark field condensor, the author reports favorable results. The demonstration of tubercle bacilli is easier, the search is less trying, more bacilli are seen, no bacilli are obscured by the counterstain, and the examination is so easy that it can be made by any practitioner.

MAX PINNER.

SHOULD THE SEDIMENTATION REACTION BE PERFORMED BEFORE BREAKFAST? H. FETZER, Beitr. z. Klin. d. Tuberk. **66**:738, 1927.

The variation of the sedimentation rate in the same patient performed before and after meals is small, so that it does not matter whether or not the reaction is performed after a period of starvation.

MAX PINNER.

THE TWENTY-FOUR HOUR VALUE OF FÅHRÄUS' SEDIMENTATION REACTION IN PHTHISICS IN THE THIRD AND FOURTH DECADE. H. FETZER, Beitr. z. Klin. d. Tuberk. **66**:742, 1927.

The author comes to the conclusion that it is important to determine not only the sedimentation rate after one and two hours, but after tweny-four hours as well. Only such patients who have a normal twenty-four hour value can be considered cured, whereas normal one and two hour values associated with a high twenty-four hour value indicate a good healing tendency but not complete arrest of the disease.

MAX PINNER.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Oct. 10, 1927

DALLAS B. PHEMISTER, *President, in the Chair*

PRESIDENTIAL ADDRESS: SURGICAL PATHOLOGY AND THE SURGEON. D. B. PHEMISTER.

Since the function of the surgeon is mainly the recognition and treatment of those diseases in which operation is necessary, a knowledge of their morbid anatomy and morbid physiology is essential for the proper execution of his duties.

Before the days of asepsis and anesthesia operative procedures were limited, and the surgeon who studied the pathologic changes in the specimens which he removed was concerned mainly with superficial lesions of the body and with such deep-seated lesions of the limbs as necessitated amputation. Hence the old terms "aussere medizin" and "innere medizin" of the German clinics. The pathologic changes that occur in internal diseases were known then largely as a result of postmortem examinations which usually revealed the primary lesion in its terminal stage. Lister's work, permitting the surgeon to enter all parts of the body, created the opportunity for physicians to study the morbid anatomy of a group of internal diseases in their earlier stages. Up to that time, such knowledge on the subject as existed had been derived mainly from incidental observations of early lesions at autopsy when death was due to other causes. Since the days of aseptic technic, the work in modern surgical pathology has been carried on by both surgeons and pathologists, and it is difficult to appraise the relative merits of each. Both have made extensive contributions to the understanding of the nature of disease as revealed by operation, and both should continue to work and cooperate in the field.

The surgeon occupies a vantage point for obtaining information that is denied to the pathologist. In the course of an operation, he is confronted in varying degrees with the necessity of recognizing and with the opportunity of investigating the local and regional pathologic changes in the disease. Naunyn said that the surgeon performs an autopsy in vivo. This is true in the limited sense that the autopsy is local or, at most, regional and that the investigation is of the gross pathologic changes only. Such an autopsy in vivo may be complete, but it is usually incomplete. The surgeon may be called on to expose, thoroughly explore and cut into diseased tissue before a decision can be reached concerning the nature of the lesion and what should be done with it, either then or at a later date. In such instances, a microscopic examination may be of great practical assistance. To make a diagnosis from frozen sections, during an operation, is more difficult than to do so later from sections of fixed tissue, and the services of a person who has had considerable and more or less continuous experience with frozen section methods are needed. For this reason, the work should be done by specialists in pathology rather than by surgeons who devote a part of their time to surgical pathology. Because frozen sections are not altogether satisfactory, the common practice of surgeons today is to perform a biopsy when in doubt after an examination with the naked eye and to defer operation until an examination of sections of fixed tissue has been completed. Strides have been made in the preparation of sections by the freezing method in connection with some of the large clinics, but opportunity for improvement still exists.

Another kind of autopsy in vivo is that in which the surgeon, feeling certain of the diagnosis, excises the organ or part with little if any invasion

of the diseased tissue. Examination of the tissues may be done by some one else than the operator, and in hospital routine this has become the established custom. As much information is lost by this procedure, however, as is lost when the organs or tissues removed at autopsy are studied by one who did not perform the autopsy. The value of the additional information about the pathologic changes gained by the operator is illustrated particularly well in mild lesions of organs which produce symptoms. Examination of the excised organ in the laboratory demonstrates little if any disease. The case of a patient who has several attacks of appendicitis recurring at irregular intervals and lasting from a few minutes to one or two hours exemplifies this. Examination shortly after an attack reveals tenderness and perhaps some rigidity at McBurney's point. An operation is performed. When the peritoneum is opened, an accumulation of clear, serous fluid is found in the vicinity of the appendix. A fibrinous exudate is not present. The appendix is normal or almost so in appearance. The regional lymph glands may be moderately enlarged. The appendix is removed. The pathologist's report may be that the organ is normal, and the surgeon may be classed among those who remove appendixes on the least provocation. Reexamination of the sections after protest may partially confirm the pathologist's report; yet a serous exudate was present, and the patient was cured after the operation. This emphasizes the importance of the pathologic tissue found at operation but not sent to the laboratory even in cases in which the primarily offending organ is removed.

Some curative operations are not in any sense an autopsy in vivo, in that the diseased tissues are neither inspected nor removed. Thus, a patient with Pott's disease of the spine may be treated by ankylosing the spinous processes or laminae of the involved region by bone grafting, and a tuberculous hip may be ankylosed by para-articular bone grafts without exposure of the diseased focus.

Since many of the pathologic changes are usually demonstrated by the surgeon at operation, it would seem logical for him to complete the work, the gross and microscopic studies of the tissues removed. But the division of labor which is necessary in order that the work may be well done renders this plan impossible as a routine procedure. The work in the department of surgical pathology in hospitals in which teaching or research is not carried on should be done by specialists in pathology. Even a special group of surgical as distinguished from "dead house" pathologists has arisen in connection with the large surgical clinics and clinical laboratories of this country. In hospitals engaged in teaching and research, the tissues should be removed surgically, to some extent at the disposal of the staff and students of the surgical clinic. These tissues may be examined in the department of pathology which extends privileges to members of the surgical staff to participate in routine or special work, or the examination may be performed in the department of surgery in cooperation with the department of pathology. From the standpoint of efficiency, the routine work might best be done entirely in the department of pathology, but it is essential that the surgeon have training in pathology, and efficiency must be sacrificed to some extent for the sake of training.

In the school of Medicine of the University of Chicago, the plan of making examinations of tissue will be tried in the department of surgery with the cooperation of the department of pathology. The tissue from the operating room will be sent in a sterile container to the laboratories of surgical bacteriology and pathology, which are in nearby rooms, in which cultures will be made when indicated and in which the section work will be done and the gross and microscopic descriptions made. The clinical clerk who has studied the patient in the ward and has witnessed the operation will participate in the examination of the tissue with a member of the department of surgery who serves as surgical pathologist. The work will be checked by the department of general pathology, and the material will be used for teaching purposes and for conferences on pathology. All gross tissue will be sent to the department of pathology, in

which they will be either stored or placed in the museum, and from which they may be withdrawn for teaching or investigation.

The research along pathologic lines carried out by clinicians has varied according to the specialty of the physicians interested in the cases. Thus, pathologic anatomical material obtained at operation has been extensively investigated by the surgeons, while pathologic physiology and biochemistry have been investigated mainly by the internists. Perhaps each group has been too little interested in the field explored by the other. Thus, Cushing thought he was expressing the reaction of the modern internist toward morphology when he said, "Why should the internist come to the operation any longer? He cannot see the sugar in the blood!" The field of pathologic physiology offers favorable opportunities for research in surgical diseases. This is well illustrated by the discoveries of Graham, Copher and Whitaker on the abnormal function of the diseased biliary tract by means of cholecystography.

Despite the extensive histologic research on operative material since the advent of modern surgery, there is still much activity in the field, and many contributions have been made by surgeons in recent years. The fate of tissues transplanted in surgical operations has been fairly well cleared up, and the results of animal experiments have been verified by the study of transplants that have been removed weeks, months or years after transplantation. Many diseases of the bones and of the joints, such as loose bodies arising from the articular surfaces and vascular disturbances of the centers of ossification in the tarsus and carpus and of certain epiphyses of long bones, have been either identified or elucidated by the work of surgeons such as Perthes, Axhausen, Freiberg and Nussbaum. Bailey and Cushing have recently published a book containing a classification of tumors of the glioma group on a histogenetic basis with a correlated study of prognosis. By an analysis of more than 400 tumors of the glioma, they have found that the tumors which produced the structure of the less differentiated cells in the developing central nervous system are more actively growing than are the ones that are composed of the more highly differentiated cells. With this better understanding of the life history of the lesions, they feel that they are able better to evaluate the prognosis and to choose the procedure which is appropriate to the particular kind of tumor which is disclosed by the operation. By his histologic studies of the thyroid gland removed from patients first operated on by pole ligation and later by subtotal thyroidectomy to whom iodine was administered during the interval, Rienhoff has demonstrated the morphologic changes produced by iodine in the disease and the relationship between the so-called primary exophthalmic goiter and toxic adenoma. The Bone Sarcoma Registry of the American College of Surgeons now contains tissues from more than 800 patients. Valuable educational work among the medical profession and some research work have already resulted from a study of this material. It should receive the attention of the pathologists of the city as the collection is now housed in the building of the College at 40 East Erie Street.

In the future, the need for surgical intervention may decrease; that is, patients with infectious diseases and malignant tumors may be treated by vaccines, antitoxins, physiotherapy or chemotherapy instead of surgically. But as long as the present day treatment prevails, it is the duty of the surgeon to be a student of morbid anatomy, as otherwise his indications for operation and the results of his therapy will be mediocre, regardless of the manual dexterity which he may acquire in the performance of operations.

ACTION OF ANTITHYROGLOBULIN SERUM. KAMIL SCHULHOF, the John McCormick Institute for Infectious Diseases.

Rats were injected with the smallest effective dose of thyroglobulin from a dog as well as with the double dose, and the resulting average increase in the metabolic rate was determined. The same increase in metabolism (within the limits of error) resulted after injection of a mixture of the thyroglobulin with its antiserum.

Injection of the thyroglobulin together with a mixture of dog serum and antiserum seemed to increase the metabolism more than injection of the thyroglobulin alone. This point will be further investigated because of the therapeutic possibilities. Injection of the mixture of dog serum and antiserum and other controls did not affect the metabolic rate.

HYPOGASTRO-ETRO-SCHISIS, SPINA BIFIDA, DIAPHRAGMATIC HERNIA AND LEFT RENAL AGENESIA IN A VIABLE FULL-TERM CHILD. GEORGE J. RUKSTINAT and JAMES D. BALFOUR.

This article will be published in full in a future issue of ARCH. PATH.

Regular monthly meeting, Nov. 14, 1927

ESMOND R. LONG, *President pro tempore, in the Chair*

WAXY DEGENERATION OF THE DIAPHRAGM AS A FACTOR CAUSING DEATH IN PNEUMONIA AND OTHER CONDITIONS. H. GIDEON WELLS.

The complete report is published in ARCH. PATH. **4**:681, 1927.

EMBRYONAE TUMORS OF THE KIDNEY. R. B. HASNER.

This article will be published in full in ARCH. PATH.

INFLUENCE OF GLYCOGEN ON THE INFECTION OF MUSCLE WITH TRICHINAE. JULIAN H. LEWIS.

One of the most striking examples of organ specificity which an infecting micro-organism can show is illustrated in trichinosis. In this disease the parasite almost exclusively infects the striated muscles of the body. The course of events which occur in the establishment of trichinosis begins with the ingestion of infected material, usually muscle tissue of pork that contains encysted *Trichinae*. The organs are liberated in the stomach through digestion of the cysts after which they pass into the intestines in which copulation and impregnation of the female worms take place. When the embryos reach maturity, the female imbeds itself in the intestinal mucosa and delivers a large number of small but completely formed young *Trichinae* directly into the lymph vessels and through these into the general circulation. It is estimated that a single female *Trichina* will expel about 1,000 young parasites into the circulation. The delivery does not occur all at once but takes place gradually, from four to five days being required for the complete expulsion of all young organisms from one female worm. Nevertheless, the concentration of *Trichinae* during this period is high enough to permit their ready demonstration in a sample of blood withdrawn either from the heart or from the peripheral circulation. With such a large number of organisms in the circulation, it is certain that some of the young parasites pass through the capillary bed of every organ in the body; yet it is only in the striated muscle tissue that they come to rest and pass through further stages of development. The understanding of this unerring discriminating selection of satisfactory conditions for existence and development, which for *Trichinae* is represented by the muscular tissue, is the problem of organotropy.

It is probable that this invasion of muscular tissue by *Trichinae* is an example of positive chemotaxis in which the organisms are attracted by the presence of some dissolved active chemical substance in the muscle. The nature of this chemical substance is not known except that *a priori* it must be

a substance devoid of species specificity, as *Trichinae larvae* manifest the same preference for striated muscles in all animals serving as hosts.

Trichinae do not invade all striated muscles in the same degree. In such muscles as the diaphragm, the intercostals, the masticatory muscles, the muscles of the larynx, the tongue and the eyes, the invasion is much stronger and earlier than in others. These muscles are characterized by their constant activity, and it was thought that this association of infection with activity might be related in a definite way to some chemical change which occurs in muscle tissue as the result of activity. One must first think of sarcolactic acid, because this is a substance which is peculiar to muscle tissue and which reaches a rather high concentration in active muscles. An attempt was therefore made to increase experimentally the amount of sarcolactic acid in muscles and to study the effect on invasion with *Trichinae*. The only way by which this could be done was to inject lactic acid or its salts into the body of the muscles. Such experiments, however, did not indicate that the amount of infection was influenced. Following these experiments an attempt was made to determine whether there was any correlation between glycogen, the predecessor of sarcolactic acid and infection with *Trichinae*. The glycogen content of a muscle is inversely proportional to its activity. The muscles usually more strongly infected with trichinosis which, at the same time, are the more active of the body muscles would be expected to have a lower content of glycogen. This was found to be true in analyses for glycogen of the different muscles in a series of guinea-pigs. The glycogen was determined by the well known method of Pflüger in which rapidly weighed samples of muscle removed quickly from the animal are hydrolyzed in boiling concentrated potassium hydroxide. The glycogen is precipitated from this hydrolysate with alcohol and is determined as dextrose after inversion with dilute acid. A representative result is given in the following figures: diaphragm, 7.22 mg. per hundred grams of muscle; masseter, 16.10; hind legs, 417.84; front legs, 480.13, and lumbar, 559.75.

The difference between the content in glycogen of the various muscles is striking. The diaphragm, of course, is in constant activity. The masticatory muscles in the guinea-pig are also in constant use because the animals will eat as long as there is something on which to nibble. The use of the legs of the ordinary laboratory animals is greatly restricted because they are usually confined to cages or to rather limited spaces in stalls. Therefore, the figures of these analyses are roughly proportional to the activity of the muscles.

If there is any causal connection between the infection of a muscle with *Trichinae* and its content in glycogen, these figures would indicate that a low concentration of glycogen is favorable to the localization and development of the organisms and that a high concentration is unfavorable. In order to test this idea further, a series of experiments were made in which the glycogen content of the tissues was either decreased or increased, and the influence of such manipulations on the distribution of *Trichinae* in muscle was observed.

The stimulation of sugar metabolism by insulin offers an excellent method to render an animal completely glycogen-free. Deposits of glycogen in the tissues of an animal are depleted in order to supply the dextrose demanded by the increased carbohydrate metabolism resulting from injections of insulin. The following experiment showed this to be true. A guinea-pig on a constant sustaining diet received 2 units of insulin per kilogram of body weight twice a day subcutaneously. At the end of the fifth day it was killed, and the muscles were analyzed for glycogen. Only traces, unmeasurable in amount, were found in any of them. Thereupon five large male guinea-pigs were infected by being fed equal amounts of muscle from a rat heavily infected with trichinosis. Three of them were fed with 200 Gm. of vegetables each day and were injected with 2 units of insulin per kilogram of body weight twice daily subcutaneously until symptoms of hypoglycemia appeared. When necessary, they were resuscitated with small injections of dextrose, and subsequent injections of insulin were given to maintain them in a condition bordering on convulsions. The

two controls were fed the ordinary laboratory diet and were not given insulin. On the nineteenth day after infection all five animals were killed. One masseter from each animal was fixed in formol and the other masseter was used to count the number of *Trichinae* which it contained. If a muscle containing *Trichinae* which are not in the encapsulated stage is subjected to high pressure between two slides or in a small press, all the organisms in the muscle will be quantitatively expressed from the tissue and can be found in the so-called "press-saft." A piece of masseter from each of the five guinea-pigs was treated in this way, and a definite amount of the fluid was spread over a ruled area on a glass slide and the organisms counted. The results of such a count are as follows:

IT7	2.45	Injected with insulin
IT8	5.0	
IT9	3.6	
IT10	0.3	Controls
IT11	0.6	

The difference between the controls and the animals that received the insulin is both regular and marked to such a degree that it indicates the true conditions in spite of the crudeness of the method. The opposite masseters, fixed in formol, were embedded in paraffin, and sections of uniform thickness were made and stained with hematoxylin-eosin. While it is difficult to enumerate *Trichinae* in a microscopic section when the organisms are young because of the difficulty of distinguishing them from muscle fibers, it was easy to see that the cellular changes in these preparations were much more marked in those from the animals treated with insulin than in those from the controls.

This experiment was repeated in exactly the same manner with another group of five animals, the only difference being that they were infected with a smaller amount of *Trichinae* with the hope that the difference between the controls and treated animals would be even more marked. They were killed on the twentieth day after infection, and counts were made of the organisms in the masseters as before. The following results were obtained:

IT17— 8 *Trichinae* per preparation	Injected with insulin
IT18—dead	
IT19—15 *Trichinae* per preparation	
IT20— 4 *Trichinae* per preparation	Controls
IT21— 0 *Trichinae* per preparation	

When sections were made, it was found that the organisms were too young and too few to produce enough histologic changes for comparison.

It is clear, then, that the depletion of glycogen in the muscle resulting from injection with insulin is associated with an increased invasion of these muscles with *Trichinea*.

An excess of carbohydrate in the diet leads to a deposit of glycogen in the liver and muscles and other tissues. This fact formed a basis of an experiment to determine the effect of the reverse conditions produced in the preceding experiments, namely, the effect of increasing the glycogen content of muscles on the degree of infection with trichinosis. If a reduced glycogen content of the muscle is associated with an increased susceptibility to invasion with *Trichinae*, an increased glycogen content which is subsequent to a high carbohydrate diet should be associated with a decrease susceptibility to the infection.

Five large guinea-pigs were infected with *Trichinae*, and three of them were fed daily with 15 Gm. of dextrose given in the form of a 50 per cent solution. The control animals were fed the ordinary laboratory diet as well as the animals given dextrose. The latter animals were also provided freely with water and green vegetables to deal with the active diuresis resulting from the ingestion of large quantities of dextrose. On the twentieth day of infection the animals were killed, and the masseter muscles were examined for *Trichinae*. It was found that the disease in all guinea-pigs had progressed to the stage of

encapsulation and that it was impossible to enumerate the organisms by expressing them as in the other experiments. On the other hand, this stage was suitable to make direct counts in histologic sections. Therefore, the total number of *Trichinae* in a 10 micron longitudinal section through the middle of each masseter gave the following results:

IT12—38 *Trichinae*.....	Fed with dextrose
IT13—26 *Trichinae*.....	
IT14—38 *Trichinae*.....	
IT15—96 *Trichinae*.....	Controls
IT16—87 *Trichinae*.....	

The results of these two series of experiments show a definite relation between the glycogen content of muscle and its susceptibility to infection with *Trichinae,* but whether this relation is causal or merely the index of a relation with another factor which varies concomitantly with the glycogen content but which is the real causative factor is a question which the present data do not answer. The latter suggestion is probably the true explanation, because, while it is an interesting fact that the invasion of *Trichinae* varies with the glycogen content of muscle, it does not explain the specificity of trichinosis for muscle tissue. Glycogen is not specific for muscles, but, on the other hand, is a widely distributed substance in the body. If glycogen were the actual determining factor in the organotropy of *Trichinae,* one would expect to find the liver constantly infected because this organ is the chief depot of glycogen. Nevertheless, *Trichinae* are never found here. Sarcolactic acid is a substance that is specific for muscles and is the end-product of the catabolism of glycogen in the muscles. Besides lactic acid, there are a number of other substances, such as the clotting proteins and the various so-called nitrogenous extractives, that are chemically distinct and characteristic for muscle tissue. Any of these substances might well be the attractive force responsible for the localization of *Trichinae* in muscle either because of a positive chemotactic action or because they furnish some peculiar nutritive substance necessary for the growth of the parasite.

THE PATHOLOGY OF POST-INFECTIOUS ACUTE TOXIC ENCEPHALITIS IN CHILDREN. R. R. GRINKER.

Brains obtained post mortem taken from the bodies of thirteen children with disorders clinically arranged as follows were studied microscopically: (1) severe diffuse brain symptoms and a definite focus of infection, (2) diffuse brain symptoms and a septicemia and (3) foci of infection and cachexia but no neurologic signs. In foci of infection are included acute otitis media, pneumonia, acute pharyngitis, peritonitis and osteomyelitis.

Grossly, nothing characteristic was found. The brains were firm and usually hyperemic on the surfaces made by cutting. Microscopically, all had gradations of similar changes. The meninges were usually distended as if by fluid and slightly thickened with connective tissue. A moderate number of infiltrated large histocytes and round cells were present. Many leukocytic thrombi were attached to the walls of the veins.

The parenchyma usually had a profound degenerative change in the ganglion cells. These were swollen, had central chormatolysis, contained small multiple cytoplasmic ringlets, and were undergoing neuronophagia. The glia cells were diffusely proliferated, especially in the deep white matter. Satellitosis was greatly increased. Mobile or gitter cells were not found, and Hortega cells were infrequent.

The vascular system was severely damaged. The capillary endothelium was proliferated so that frequently obliteration resulted. The endothelial cells were swollen and pyknotic. The formation of new vessels was frequent. Mesodermal infiltration of the vessels or parenchyma was not found.

The absence of infiltration by mesodermal elements, the vascular proliferative changes and the parenchymatous damage lead to the conclusion that microbic invasion of the brain or meninges had not taken place but that a toxic reaction was present.

THE EFFECTS OF ROENTGEN RAYS ON THE KIDNEY. DAVID A. WILLIS and ALBERT BACHEM.

Irradiation of the kidney produces a progressive degeneration of the tubule, with replacement by newly formed connective tissue and without signs of regeneration of the broken-down tube. The glomeruli, in spite of the marked tubular changes, remain practically unaltered, their reduction in size and distortion being produced secondary to other changes. In the chronic glomerular nephritis as seen in man, the glomerular changes are primary and the tubular changes secondary. In the irradiated kidney this process is exactly reversed, the tubular degeneration being primary, this being followed by scar tissue formation, obliteration of the capillaries and finally glomerular atrophy. The contracted kidney thus produced is therefore the end-result of a nephrosis.

The complete report will be published in the *American Journal of Roentgenology.*

NEW YORK PATHOLOGICAL SOCIETY

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DAVID MARINE, *President, in the Chair*

THE HISTOLOGY OF LESIONS OF BLACK TONGUE IN THE DOG. JAMES DENTON.

The lesions producible in the dog by feeding on a diet deficient in Goldberger's P.-P. factor were described and illustrated. The lesions were primarily degenerative ones of subepithelial supporting tissues of the mouth, tongue, pharynx, esophagus, colon and skin. Lesions from human pellagra material from the same tissues and organs were shown to illustrate the similarity of the lesions in the two diseases.

DISCUSSION

LOUIS GROSS: I should like to hear the specific diet these dogs were given. Exactly what is meant by saying that these animals were vitamin B deficient but not on a sharp vitamin B deficiency diet? When rats are put on a diet deficient in vitamin B they begin to starve themselves, and one gets pictures which are difficult to distinguish from starvation. I should like to hear whether it was noted just how often these lesions were found, how much weight the dogs lost, and whether comparative studies have been made without a vitamin B deficiency but with the same amount of relative starvation to determine whether the pathologic picture is characteristic or not. I was much interested in the pathologic condition of the alimentary tract which Dr. Denton has shown. Kramer in England showed pictures of the alimentary tract in rats with vitamin A deficiency, and I was not able to confirm his results. Possibly the differences may have been in the age of our animals, the differences in the diet, or one of us may have been wrong. I also worked on a fairly large series of rats fed on a diet deficient in vitamin B, and was unable to find any lesions like those just described in the intestinal tracts.

JAMES DENTON: I did not give the details of the feeding experiment, as they will be published by Dr. Goldberger in a government bulletin. The material was given to me as unknown material, and I know little about the experimental part of the work. We have had experience with simple starvation, and we have made a serious effort to discriminate between simple starvation and the disease I have described. These lesions, aside from the

necrotic stomatitis, were found in dogs in good states of nutrition. Dogs, weighing 12 or 13 pounds (5.4 or 5.9 Kg.) had lost only 2 or 3 pounds (0.9 or 1.4 Kg.). They were bright and lively when killed, and they did not show evidence of starvation. We have also studied rat tissues, and the reactions in the two animals do not appear identical.

The intestinal lesions do not appear in the early stages of the disease, but appear after the dogs have been on the diet two, and up to four and a half months. I observed the dogs clinically at intervals, performed the autopsies and selected the tissues best adapted to show the different phases of the lesions. The diet would be classed as one deficient in vitamin B. My impression is that it was low in protein and high in carbohydrates.

In a series of twenty-one dogs allowed to die of the disease, the lesions were present in all. The ones I have shown are from a series of thirteen dogs killed in the early stages of the disease. Proper controls were examined also. There are apparently some differences between the reaction in the dog and in some other laboratory animals — the inability to produce scurvy in the dog illustrates this.

DAVID MARINE: Am I right in saying that Mendel was able to cure black tongue by adding butter to a diet that would otherwise produce the disease in dogs?

JAMES DENTON: I do not know. I know that yeast cures it readily, and that the animals may be kept in a sort of larval stage of black tongue by the addition of small amounts of yeast to the diet.

DAVID MARINE: The question that came up was whether there was a vitamin A deficiency, but cod liver oil would not cure it, while butter relieved it.

JAMES DENTON: It appears to make a difference whether the yeast is autoclaved or not.

EXPERIMENTAL INTESTINAL HYPERTROPHY. BENJAMIN N. BERG and JAMES W. JOBLING. (From the Department of Pathology, College of Physicians and Surgeons, Columbia University.)

In conjunction with observations on the effects of prolonged experimental incomplete obstruction of the duodenum, an opportunity was afforded to study the details of intestinal hypertrophy.

The method which was employed to produce the chronic obstruction in dogs was as follows: A pedicled flap was made of the posterior sheath of the rectus abdominis muscle. A segment of the duodenum about 15 cm. from the pylorus was chosen for the site of the obstruction. Through a small opening in the mesentery, the fascial flap was wound around the duodenum in the form of a sling, and the lumen of the duodenum was constricted.

Thirteen dogs were studied for periods extending from fifty-one days to one year and forty-five days. Varying degrees of dilatation and hypertrophy of the duodenum above the stenosis were observed. In order to determine the degree of hypertrophy that occurred, the width of the intestinal wall above the stenosis was compared with the width below the stenosis. In addition, the separate muscular layers were measured and compared in order to determine the relative hypertrophy of each component. The segments of the duodenum which were selected for comparative study were obtained at the level of the sphincter of Oddi and a few centimeters below the site of the obstruction.

It was found that the average increase in the total width of the muscularis above the obstruction was 2.17 times greater than that of the muscularis below the obstruction. A study of the separate muscular components, however, showed that the inner circular layer contributed to a greater extent to the hypertrophy than the outer longitudinal layer. The average increase of the inner layer was 2.28 times; the average increase of the outer layer was 1.85 times. Moreover, since the inner layer normally is from 2.5 to 3 times thicker than the outer one, the absolute increase of the former was many times greater than the increase of the latter.

No correlation could be determined between the degree or duration of the stenosis and the extent or distribution of the hypertrophy. This was due to factors that could not be measured or controlled accurately, such as individual variations in muscular tonus and contractility, and unavoidable differences in the degree of obstruction that was produced.

A third or specialized circular layer, heretofore not described, which was found just internal to the inner circular layer, was also hypertrophied.

The studies of Carey concerning the effects of tensional stresses on the arrangement of the smooth muscle of the intestine in the embryo may have some application to an understanding of the physical forces which were responsible for the greater hypertrophy of the inner circular layer compared with the outer longitudinal layer in chronic intestinal obstructions.

DISCUSSION

SAUL RITTER: I should like to know whether Dr. Berg found toxic degenerative nephrosis associated with the experimental high intestinal obstruction.

DAVID MARINE: Was the muscularis mucosa hypertrophied? It looked so in the sections.

LOUIS GROSS: Did you make some effort to standardize your preparation when you made the measurements? I assume that they were made in the fixed state. As Dr. Berg mentioned in his paper, there are certain factors that are difficult to control, for instance, the tonus; a piece of intestine is taken and stretched out, and fixed in that condition, or if it is put in the cold, it will contract and be fixed in that condition. It makes enormous differences, not perhaps between the outer and the inner muscular coat, but if one wants to compare one intestine with another the difference will be great. I had some experience along those lines, and I found that if I cut off a piece of tissue relatively the same distance from the pylorus, put the tissue on ice, kept it at a certain constant temperature, and fixed the tissue at this temperature, I was able to make pretty good comparative measurements.

PAUL KLEMPERER: What did you find in those stenosed parts?

BENJAMIN N. BERG: There was no evidence of nephrosis. Lesions were found in the kidneys of most of the dogs. The lesions were principally interstitial, however, and were not considered significant due to the occurrence of similar changes in the kidneys of so-called normal dogs, kept under favorable laboratory conditions.

The muscularis mucosae was not hypertrophied.

Although variations in the tonus of the musculature at the time of fixation would influence the measurements of the total width in different animals, the comparative measurements of the total width and of the separate muscular components above and below the stenosis would be relatively accurate for each dog. The ratio would not be affected appreciably. The intestine was fixed in Zenker's fluid, in the living state (with the animal under ether narcosis) or immediately after death.

At the site of the stenosis, the mucosa was intact and did not show atrophy. The muscularis was irregular and atrophied.

AN IMPORTANT ANASTOMOTIC VESSEL IN THE AURICLE OF THE HUMAN HEART. M. A. KUGEL.

In a study of fifty normal hearts, a large anastomotic vessel joining the right and left coronary arteries was observed in the auricle of the human heart. Except for brief mention by the author with Dr. Louis Gross in an article on the gross and microscopic anatomy of the blood vessels of the valves of the human heart, a previous report has not been found in the literature dealing with this vessel.

On account of its constancy in location and structure, this vessel will be referred to as the arteria anastomitica auricularis magna. In 66 per cent of

the cases it arises from the left circumflex artery from 1 to 2 cm. below its mouth and plunges directly into the wall of the left auricle. It then pursues a wavy course medially within the anterior wall of the left auricle from 0.5 to 1 cm. above the insertion of the aortic leaflet of the mitral valve. It proceeds backward into the interauricular septum for its entire length, and near the crux of the heart unites directly or by intermediary smaller twigs with the posterior distribution of the right circumflex coronary artery. In a smaller group of cases, the vessel turns abruptly on itself in the interauricular septum and passes forward to the anterior wall of the right auricle, piercing it to unite directly or by intermediary smaller twigs with the anterior distribution of the right circumflex coronary artery or its branches (25 per cent in this series). In a very small group of cases, the vessel is of a more diffuse distribution in the anterauricular septum.

The arteria anastomotica auricularis magna sends branches in the auricular musculature toward the base of the aortic leaflet of the mitral valve. These branches are often united by an anastomotic arch. Furthermore, these twigs arise from the same site as do the vessels found in the aortic leaflet of the mitral valve (when they exist). What is more significant, these branches, either with or without the anastomotic arch, have been seen at various levels within the auricular musculature, at the base of the valve, and within the valve substance at times reaching the line of closure.

The arteria anastomotica auricularis magna also supplies blood vessels at times to the cusps of the aortic valve, chiefly the left and right posterior cusps.

As it passes within the anterior wall of the left auricle the anastomotic vessel bears an intimate relationship to the left posterior portion of the aorta and sends blood vessels upward, forward and inward, to terminate either in the commissures or for some distance within the insertions of the aortic cusps. The commissure between the left and right posterior cusps is in intimate relationship to the aortic leaflet of the mitral valve and receives the greatest blood supply from the anastomotic vessel. At the same time the anastomotic vessel sends a large number of vessels to the base of the posterior portion of the aorta which anastomose freely with the vasa vasorum of the aorta. Besides supplying blood to this area it serves as a wide anastomotic channel between the right and left coronary artery, and it is of interest to note that in several hearts which were the seat of arteriosclerotic coronary artery disease, this vessel was of unusually large caliber.

Its intimate relationship to the blood supply of the mitral and aortic valves, as well as of the commissures and the aorta, may be one of the factors concerned with the localization of lesions in the commissures such as those found in rheumatic disease, subacute bacterial endocarditis and syphilis.

(A detailed report of this work will appear in a forthcoming number of the *American Heart Journal.*)

BLOOD VESSELS IN THE VALVES OF NORMAL HEARTS (SUMMARY FROM A STUDY OF THE HEARTS FROM 700 AUTOPSIES). SAUL A. RITTER, LOUIS GROSS and M. A. KUGEL.

The blood vessels as they exist in the aortic leaflet of the mitral valve of some human hearts can be subdivided architecturally into two groups, the complete form and the incomplete forms.

The complete form (probably representing a persistence of the fetal architecture) is usually made up of an anterior, a posterior and an intermediate branch. These branches, after coursing for some distance toward the closing edge of the valve, are united by an arcuate arch. The latter frequently gives rise to a brushwork of finer vessels which descend to the line of closure. The anterior, posterior and intermediate branches almost invariably arise from the anastomotic loop (arteria anastomotica auricularis magna), which runs in the interauricular septal muscle to join the left and right coronary arteries of

their branches (as described by Dr. M. A. Kugel). The incomplete form presents a series of gradations in regression or development of this vascular structure.

In nonvascularized valves, the arteriae valvulares are evidently aborted and often terminate in the auricular musculature near the base of the valve, usually forming an arch. In a previous publication, two of us, reported that seven of eighty-five hearts showed complete vasculature of the aortic leaflet of the mitral valve, all of which, however, revealed a coexisting endocarditis. Blood vessels have also been found to exist in the aortic, tricuspid and pulmonary valves. They occur relatively infrequently. They will be reported and described in a later publication.

In this paper we propose to outline briefly the results of our studies on the hearts from 700 autopsies. The coronary arteries were injected with a barium sulphate gelatin mixture, under standardized conditions and technic, as described by Dr. Gross. Of the 700 hearts studied, 123 revealed blood vessels in one or more valves. Fourteen of the hearts were found to be normal after thorough clinical and pathologic examination. Six of the fourteen normal hearts presented the complete type of mitral valve vasculature and eight presented the incomplete form. In no respect, either clinically or pathologically, could evidence be found that the endocardium had been subject to an inflammatory lesion or that the myocardium had at any time been the seat of any inflammatory pathologic process. Numerous sections were made from the auricles, ventricles, papillary muscles, valves and base of the aorta, especially those sites at which Aschoff bodies are most frequently found. The specimens were fixed in alcohol and formalin and were stained with hematoxylin and eosin, with Unna, Pappenheim, with van Gieson's stain, with the MacCallum-Goodpasture stain, and with Weigert's elastic tissue stain. Search was made for Aschoff bodies, Bracht-Waechter lesions, MacCallum's auricular lesions, the lesions described by Klotz, von Glahn and Pappenheimer, for all foci of inflammation, pericarditis and also for the commissural lesions described by Grant and Lewis. Studies of all the other parenchymatous organs were also made with especial reference to the kidneys and spleen.

With one exception, as far as we were able to ascertain, there was no previous history of rheumatic fever, chorea, arthritis or repeated attacks of tonsillitis. In the exceptional case, there was a history of scarlet fever in childhood.

Of the 123 hearts with blood vessels in one or more valves, 109 hearts could be classified into two groups:

GROUP I.—This group was composed of seventeen hearts, which, although appearing grossly normal could not be accepted as normal because careful histologic studies revealed occasional small foci of inflammation or accumulation of inflammatory cells in the myocardium, valves of the heart or pericardium.

GROUP II.—This group was composed of the remaining ninety-two hearts, which had blood vessels in the valves and which were associated with definite valvular endocarditis, past or present.

The following observations lead us to believe that blood vessels found in the valves of some human hearts are of noninflammatory origin:

1. The constant origin of these arteriae valvulares from the anastomotic arch (arteria anastomotic auricularis magna) as described by Kugel in another paper. This vessel joins the right and left coronary arteries.

2. The constant occurrence of an aborted auricular arch and variations in the level of this arch to a site within the valve leaflet.

3. The constant characteristic architectural distribution of the arteriae valvulares.

4. Histologic demonstration of arterial and venous structure of these vessels. the former possessing definite intima, internal elastica and muscular media, and the latter showing a delicate muscular structure.

5. Demonstration of a venous return in the valves to the coronary sinus of the heart by means of injection of the coronary sinus with barium sulphate gelatin mixture.

6. Striking similarity of vascular architecture that has been found to exist in the normal aortic leaflet of the mitral valve to that found in certain lower animals as cattle, sheep and swine.

7. The occurrence of vessels in the valves of the fourteen normal hearts described. These hearts were judged to be normal only after thorough clinical and pathologic examination.

(A detailed report of this work will appear in a forthcoming number of the *American Heart Journal.*)

DISCUSSION

E. LIBMAN: I should like to ask Dr. Kugel which one of the commissures usually receives the most blood supply from the artery which he has so carefully described.

M. A. KUGEL: Apparently the greater blood supply goes to the commissure between the right and left posterior cusps. The commissure between the right posterior and the anterior cusp receives less, and the commissure between the anterior and the left posterior cusps receives the least amount of blood.

E. LIBMAN: That is what I expected might be the case. In the first place, it is clear from the extensive studies presented by Drs. Ritter, Gross and Kugel, that there are preformed vessels in the valves, particularly in the aortic leaflet of the mitral valve—not due to previous inflammatory conditions. The exclusion of cases in which the valves showed only a small number of lymphocytes makes the conclusions still more valuable. I will not discuss the part that the vessels may play in endocarditis, and in predisposing to it.

The studies of Dr. Kugel are of interest in connection with the commissure lesions of subacute bacterial endocarditis. In 1923, Lewis and Grant described lesions of the commissures of the aortic valve which they believed represented healed lesions of subacute bacterial endocarditis. I had overlooked these lesions. Although Lewis and Grant did not prove that these lesions represented the results of subacute bacterial endocarditis, by looking for healed embolic glomerular lesions in the kidneys, I am convinced that their opinion is correct. In one case I found a lesion of one commissure of the aortic valve which was partly healed, and partly active.

In rheumatic endocarditis one often finds a commissure lesion which binds adjacent flaps together below the attachment to the aorta. In syphilis, as Scott has pointed out, there is apt to be a separation of the commissure. According to his description, the syphilitic virus passes from the aorta to the flaps of the valves by means of the vessels in the commissures. In subacute bacterial endocarditis the commissure lesion consists not only of a fusion of two flaps to each other, but to the wall of the aorta. If one looks over a number of specimens, it is found that the commissure which is most often involved is the one which Dr. Kugel has described as being the one usually the best vascularized by the artery which he has described—the arteria anastomica interauricularis magna. Occasionally one finds an instance in which the lesions in a case of subacute bacterial endocarditis are limited to the aortic flap of the mitral valve, and one or more commissures. In a certain number of cases of what formerly would have been considered ordinary aortic stenoses and obstructions, one finds these old, healed lesions of the commissures.

The occurrence of healed lesions of the commissures, associated with involvement of the aortic flap of the mitral valve, lends a peculiar significance to the observations reported by Dr. Kugel.

B. S. OPPENHEIMER: Does this new interauricular anastomotic artery described by Dr. Kugel also supply the bundle of His or the auriculoventricular node? If so, it is important and will have to be considered in studying the correlation between electrocardiographic results and the anatomic lesions. In

the course of such a study in 1913, Prof. H. B. Williams and I published a case of prolonged incomplete heart block without lesion of the bundle of His and with frequent changes in the idioventricular electrical complexes. At autopsy both the descending and the circumflex branch of the left coronary artery were found completely obstructed within a short distance of their origin. Complete occlusion of the main branch of the right coronary was not found, but its posterior descending branch was completely obstructed beginning about 0.5 cm. from its origin and extending for a distance of about 1.5 cm. A study by means of serial sections of the bundle of His did not reveal any lesion to explain the block, and its artery, although definitely sclerosed and stenosed, was not found thrombosed. We stated in conclusion that "complete heart-block without anatomic lesions in the auriculoventricular system may possibly be of neurogenic or of circulatory origin, or it may be ascribed to chemical agents, to asphyxia, or to some hindrance to the passage of impulses from the terminal arborizations of the conducting system to the ventricular musculature." Since then we have had several instances in which it seemed probable that the heart block was due to circulatory disturbance, but, of course, we were wholly unaware of this arterial supply described by Dr. Kugel. If this newly discovered artery parallels the usual artery to the auriculoventricular node and bundle of His, it will be important in the study of similar cases of heart block.

E. LIBMAN: What Dr. Oppenheimer has said is of interest, and I have made casual observations on the association of auriculoventricular block and stenosis of the arteries.

Within the last couple of years Giraudel, working in the clinic of Professor Vaquez, has published observations on auriculoventricular block due to obstruction of the coronary arteries. I had the opportunity of seeing some of this work last summer, and as far as I could make out there seemed to be no doubt that auriculoventricular heart block can be produced by narrowing the vessels, without there being present a local lesion in the bundle. I have evidence that sino-auricular block can be caused in the same way.

LOUIS GROSS: The question has often been raised as to whether these vessels were really embryonic or postinflammatory. One is struck by the fact, as Dr. Ritter has pointed out, that of the 123 hearts which showed the blood vessels in the valves, 92 were definitely associated with a valvulitis of some sort. He said that 17 hearts did not have definite valvulitis, but we excluded them from the series of normal hearts because we found a few scattered lymphocytes. We wanted to be particularly cautious about what we called normal hearts. In spite of this caution, perhaps these fourteen hearts really had been the seat of an endocarditis. Perhaps it is a peculiar kind of endocarditis or valvulitis which attacks the heart and then completely disappears, leaving nothing but the blood vessels. If so, it weakens our claim as to the non-inflammatory nature of these blood vessels. I want to point out that this is not a mere academic question. If they are of noninflammatory origin, they may have something to do with lesions which occur in the valves. If they follow inflammatory disease of the valves, they are merely of interest pathologically, and have no practical importance. There is no possible way that I know of proving that these vessels are noninflammatory. As it is, we must judge from other observations which we can make, such as those Dr. Ritter has presented. On the basis of the comparisons which we have made, we feel that these blood vessels are found fairly frequently in cattle and in swine. Even the human being has these blood vessels comparatively frequently. If one considers the 14 hearts as being the only normal hearts with blood vessels in the valves of the 700 studied, there are still 2 per cent of persons with blood vessels in the valves of their hearts who die in a hospital. The whole series of patients with endocarditis with blood vessels in the valves of the heart after death may be omitted. I just want to point out to those who still think that these vessels may be postinflammatory that one must then assume that the

inflammatory lesion has disappeared and left only these vessels. One is left with the extraordinary alternative that at least 2 per cent of persons develop a severe valvulitis at some time during life which produces these remarkable vessels, arteries and veins of a characteristic architecture and a characteristic histologic structure. In spite of its severity, we must assume that this valvulitis has not produced any clinical manifestations in these persons. Their past histories are normal, and the process has apparently completely regressed and left only blood vessels in its course. It seems to us that this alternative is even more difficult to accept than the other — that these blood vessels are of noninflammatory origin. I do not want to go into detail as to what the significance of these blood vessels may be. Dr. Libman has touched on that, and he is more able to judge of the application of these observations than I am. If we can satisfactorily decide that these vessels do not owe their origin to inflammation, we may be able to show in the future that the unfortunate persons who have such vessels are predisposed to valvulitis. We do not want to deny that capillaries of granulation tissue type will develop from these preexisting blood vessels, but we want to distinguish between these granulation capillaries and these blood vessels which probably owe their origin to their embryonic derivation.

In regard to Dr. Oppenheimer's question about the anastomosis, there is a distinct and rich anastomosis between those blood vessels described by Dr. Kugel and those which supply the auriculoventricular node. It is conceivable that as there is this anastomosis, and the mitral is the most frequently involved valve, some of the blood supply might be taken away if any obliterative lesion should occur in this vessel, and we can conceive of the different variations up to complete obstruction to the supply of the auriculoventricular node.

B. S. Oppenheimer: Have you made any observations on the blood vessels in the valves of the fetus or of infants?

Louis Gross: Unfortunately, I must answer this question negatively. So far as the fetus is concerned, and this is an old observation, all the valves up to the fourth fetal month have blood vessels. Of this there seems to be little doubt. We have always seen it in these young fetal hearts. It is a difficult piece of work to show it. I cannot tell you about the structure, whether it shows the anterior, posterior and intermediate branches and the rather constant architecture that Dr. Ritter has shown. I would not expect that infants' hearts would show these blood vessels any more often than the hearts of adults. The probabilities are that if they are going to disappear, they will disappear around the fourth fetal month. The only way to settle this question is to study a large amount of material. The autopsy material that comes to Mount Sinai Hospital is selected material. A large number of the patients are patients with cardiac disease of long standing, and naturally we find vessels in a great many of these cases. In order to find them in children in anything like the proportion found in adults, one would have to study a large amount of material. We have been making efforts to obtain infants' hearts from other hospitals to study this question.

Paul Klemperer: How many of the ninety-two discarded cases show the constant architecture?

Louis Gross: Ninety-two hearts were condemned on account of a distinct valvulitis, all of which had these blood vessels, either in complete or incomplete form. The complete form is the type which Dr. Ritter showed, with the anterior, posterior and intermediate vessels, and an arcuate arch. The incomplete form is that in which there is an anterior or a posterior, but never an arcuate, arch. We believe there has been either incomplete regression or incomplete development of the arch. In most cases the blood vessels are of the incomplete type; I have the impression that about 60 per cent were of the complete type.

Book Reviews

La Vaccination Preventive Contre La Tuberculose Par Le "BCG." By A. Calmette. With the Collaboration of C. Guérin, A. Boquet and L. Nègre. Price, 22 francs. Pp. 250. Paris: Masson et Cie, 1927.

This is a valuable monograph, perhaps not so much for the purpose for which it is written, which is to prove the efficacy of "BCG," but for summarizing the efforts which have been made to procure, by protective inoculation, the prevention of the most prevalent and fatal disease of man — tuberculosis.

Protective inoculation has been known for many centuries. It was made practical at the end of the eighteenth century by Jenner who inoculated with the living virus of cowpox to protect against smallpox. From that time on there have been frequent efforts to apply the principle involved to many other diseases and naturally to tuberculosis. Calmette has fairly epitomized the efforts which have been made in this direction in every country with tuberculin, dead bacilli, modified bacilli, living bacilli, attenuated bacilli; with bacilli orginating in one animal for which they may be virulent and inoculated in other animals comparatively insusceptible; with strains avirulent in the same type of animal from which the strain was gathered; and by means of acid fast bacteria avirulent for all animals, and many other methods.

With this historical review, Calmette commences the study of the modes of infection in very young animals. Calling attention to von Behring's proposal in 1903, that adult pulmonary tuberculosis originates in the digestive tract as a result of ingestion in infancy of tubercle bacilli, Calmette leads up to his own experiments and those of others in proof of this premise. While this explanation of much clinical tuberculosis may be true, at the same time it is equally true that infection by way of the conjunctiva and nasal mucous membrane, and the respiratory tract through the tonsils and lower respiratory mucosa also plays an important part in tuberculosis.

There is a special temptation to turn to Chapter IX in which, with a frankness worthy of the author and a true scientist, he sets down the objections and criticisms offered against inoculation of the new-born with "BCG," and his answers. In reading this chapter one is inclined to turn again to the historical summary in the earlier chapters giving the reasons for vaccination with "BCG" and to try to judge from the work of many experimenters what is the truth about the vaccination proposed and used so freely by the authors of this book.

One can scarcely look on "BCG" as other than an avirulent organism of the tubercle type even though modified as the authors claim by growth on bile medium over a long period of years. It is doubtful whether it differs in vaccinating power from other avirulent tubercle organisms, or whether the experiments with it differ from those with other strains of tubercle bacillus avirulent for a given animal family against infection with an organism from another animal family. The evidence given here is not convincing in spite of the extensive experiments on human beings. It is difficult to believe today in the attenuation of a fixed strain as opposed to a conception of the survival of avirulent strains in the culture which may have originally contained one or more strains — a condition the occurrence of which has been satisfactorily proved. It would seem certain that Calmette in "BCG" has a strain avirulent for most animals, although some investigators have found it pathogenic for guinea-pigs, and even in cattle it may produce cold abscesses. Weill-Halle found that it may produce cold abscesses in infants. Of course dead tubercle bacilli will do this also but the "BCG" organism is a living organism pro-

ducing in its early days the local lesions characteristic of tuberculosis. Such lesions do cause some immune process in the body as Koch showed in what is known today as the Koch phenomenon.

It has been maintained by Theobald Smith that the proper place to study infection and protection of animals from tuberculosis is in the bovine family since tuberculous infection in it has many points of similarity to the human disease and can be subjected to a rigid control not possible in the human family. In his experiments on protection in cattle, Calmette used as hypodermic injection, but selected ingestion as the means of inoculating children. The only experimenter whose work can be considered consistent in point of administration is that of Weill-Halle who gives children the injection subcutaneously. The number of children, thus treated, however, is not sufficient nor is the length of time nor the controls sufficient to justify any conclusions yet from this more exact method of administration.

The feeding of the living organism as proposed by Calmette for children has really little to sustain it. There is evidence to all who have worked in this field that small doses of avirulent organisms taken by mouth in laboratory animals do not produce tuberculosis. Furthermore, it requires comparatively large doses of virulent organisms (as shown by Calmette, Vallée and others) to produce tuberculous infections in animals and the evidence at hand all points to the necessity for tubercle formation from dead or living organisms to produce any degree of immunity. To utilize the results of subcutaneous or intravenous inoculation as justification for ingestion of avirulent organisms as a means of vaccinating children does not seem justified at the present time. One certainly could not accept the results of vaccinating newly born infants simply on the basis of large numbers, without having an equal control under exactly similar circumstances in the unvaccinated over a much longer period of time, that is, one or two generations of infants under the same conditions.

A much safer course of experimentation is being pursued in England (*J. A. M. A.* **89**:802 [Sept. 3] 1927), in the United States and in Canada—in Alberta, under the direction of the National Research Council of Canada—to test the efficacy of vaccination with "BCG" in cattle, as Theobald Smith has suggested. It would seem wise for all those interested in the welfare of the people to await the results of these carefully controlled experiments before going wholesale into vaccination of newly born infants.

The literature on "BCG" is rapidly increasing, but little that partakes of exact experimental requirements is contained in it. It is possible that much good will come from the studies which Calmette has stimulated but it may be in a different field from that of protective inoculation by ingestion of avirulent living organisms.

A Textbook of Pathology. By Alfred Stengel, M.D., Sc.D., Professor of Medicine, University of Pennsylvania, and Herbert Fox, M.D., Professor of Comparative Pathology, and Director of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania. Eighth edition. Price, $10. Pp. 1,138, with 552 text illustrations, many in colors and 18 colored plates. Philadelphia: W. B. Saunders Company, 1927.

This book has been before the medical profession for twenty years, during which time it has been reprinted and reedited about nineteen times. Such a reception indicates a large demand for a work which gives a little information about each of a great variety of things, whether or not this is sound pedagogy. In their preface to the latest edition, the authors say: "Despite the view sometimes entertained and expressed that pathology either calls for more than a single volume or should be presented in connection with clinical discussions in a system of medicine, our feeling is that details of morbid anatomy and physiology, and

to a reasonably sufficient extent, of etiology, can and should be gathered in a convenient form for students and that there will always be use for single volume textbooks on pathology in paragraphic form."

If there is anything a single volume textbook covering, as this one does, general pathology, special pathology, bacteriology, parasitology and immunology, cannot possibly do it is to give details. The most it can do is to intimate the existence of many conditions, and to hint at their character. The book does this perhaps as well as another of its type, but it is difficult to see how a student can get a mental picture of any of the enumerated conditions, or any understanding of their pathogenesis or correlations from the few words devoted to each. When every medical student has a textbook specifically devoted to bacteriology, what use will he make of a section on bacteria of fifteen pages, and how much understanding of immunity from another fifteen pages on this complex subject, even if the sacred diagrams of Ehrlich are faithfully reproduced. With textbooks on dermatology accessible to practically any one who would use a textbook of pathology, of what value is a discussion on the pathology of the skin which covers the lesions of the sweat glands, nails and hair, all three on less than one page — each disease treated somewhat less fully than a student's medical dictionary would define them? It might seem that the teaching of pathology in American medical schools should have passed beyond the stage that books of this sort represent, but the fact of eight editions speaks emphatically against such utopian assumption. The thought of nineteen reprintings in twenty years makes the reviewer feel humble — he could not possibly write a textbook of pathology that would make such a record, so probably his ideas on what a textbook should be are all wrong.

HYPOTENSION. By ALFRED FRIEDLANDER, College of Medicine, University of Cincinnati. Price, $2.50. Pp. 216. Baltimore: Williams & Wilkins Company, 1927.

The author does not attempt to solve the many questions involved in hypotension. He does not advance any special theory of his own. He aims rather to present a critical analytic study of low blood pressure in the literature, and he has done this in a satisfactory manner. One should not be repelled by the frank statements of the preface and the first few pages. Here, one is told that "There is no agreement among clinicians or physiologists as to what constitutes hypotension." "There are numerous gaps in our knowledge of the causes of low blood pressure." "For certain types of hypotension no adequate explanation has yet been found." But perusal of the book shows that much knowledge concerning this subject has accumulated, even though much of it is still more or less confused and of uncertain significance. Friedlander's review should serve to stimulate further interest in this important condition. Something of the plan of the work may be seen from the titles of some of the chapters, or rather paragraphs, for there is really no division into chapters: Temporary hypotension; hypotension in acute diseases; hypotension in chronic diseases; hypotension due to certain mechanical factors; the action of tissue extracts, glandular extracts, and certain drugs on blood pressure, essential hypotension; hypotension due to malfunction of the factors which normally maintain blood pressure; hypotension in relation to endocrine disorders.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. A WORKING MANUAL OF CLINICAL PATHOLOGY. By J. C. TODD and A. H. SANFORD. Sixth revised edition. Price, $6. Philadelphia: W. B. Saunders Company, 1927.

With the collaboration of Sanford, Todd has considerably enlarged this useful book. Small technical points have received the due attention which is so necessary. Simple tests are given precedence. It might have been well, however, to eliminate those tests which are of no value. The authors them-

selves declare, for instance, that Ruhemann's method for the estimation of uric acid is far from accurate, and yet they believe that it will probably answer for many clinical purposes. It is difficult to imagine any clinical indication for this method except the "ut aliquid fiat"—a decidedly immoral purpose in diagnosis. Among the tests for renal function a better concentration test might have been selected, but this and a few similar minor points do not detract from the value of the book which is intended chiefly as a technical aid. The animal parasites are discussed in an excellent manner, and the numerous good illustrations are of much more value than the schematic pictures in old books used to be. The book really is a working manual, as its subtitle indicates.

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